Menopause Management in 2019: *everything you need to know!*

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Disclosures:

- I have no commercial interest in any of the products I will discuss today
- I will discuss both on- and off-label uses of drugs
- My perspective is solely that of a clinician and educator

Learning Objective:

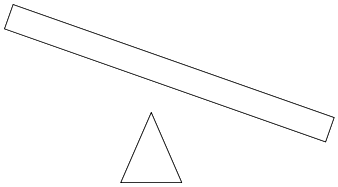
- After this talk, you will know important guidelines regarding hormone therapy use in various clinical settings

NOT…

BUT…

Balancing Benefits and Risks

The WHI was ***not*** designed to address the **benefits** of hormones for symptomatic women



The WHI is the ***best*** medical evidence we have to date concerning the **risks** of hormone therapy

Individualizing:

- Risks differ for different women depending on
  - Dose
  - Duration
  - Route of administration
  - Timing of initiation
  - Progestin or not?
- Periodic reevaluation

The Seven Dwarves of Menopause

Which are caused by menopause?
Which can be relieved by hormones?

- Sweaty
- Sleepless
- Bone-dry
- Grumpy
- Anxious
- Dopey
- Sexless

Benefits of Hormone Therapy for symptoms

Unequivocal

- Hot flashes and night sweats
- Vaginal dryness

Probably Beneficial

- Poor sleep
- Adverse mood

Conflicting/ Inadequate Data

- Sexual function
- Urinary incontinence
- Joint pains
- 'Brain fog'
- Changes in body composition
- Skin dryness/wrinkling

It's not just symptoms, it's long term health too!

Essential to know:

Menopause: The Journal of The North American Menopause Society
Vol. 24, No. 7, pp. 728-753
DOI: 10.1097/GME.0000000000000921

POSITION STATEMENT

The 2017 hormone therapy position statement of The North American Menopause Society

Abstract

The 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) updates the 2012 Hormone Therapy Position Statement of The North American Menopause Society and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2012 Position Statement, evaluate new literature, assess the evidence, and reach

How We're Going to Think About This Today:

CASES

then POSITION STATEMENT

Patient #1

- 45 yo woman
- Periods are heavier and more unpredictable, skips a period now and then
- 10 hot flashes per day
- 3 night sweats per night
- Using dong quai and evening primrose oil

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Cycle Control in Perimenopause

- HT not usually effective for perimenopausal irregular bleeding because these women need **CYCLE CONTROL**
- HT dosages are about ¼ the strength of the lowest dose oral contraceptive (not enough to control irregular bleeding)

Is it weird that she's hot flashing so much at such a young age?

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Natural History of Hot Flashes

Transition Stage	% affected*	Age
Premenopause	20-45%	<45
Pre- to-Early Perimenopause	25-55%	45-47
Early-to-Late Perimenopause	50-80%	47-49
Late Peri-to-Postmenopause	35-75%	49-55
Late Postmenopause (>5yr)	16-44%	56+

References:
Barnabei V et al. Obstet Gynecol 2002; 100:1209-18
Gold EB, et al, Am J Pub Health 2006; 96:1226-35
Politi MC, et al. J Gen Intern Med 2008;23:1507–13.

Patient #1 how to manage?

- Consider endometrial sampling
- Stop the dong quai and evening primrose oil
- Low dose monophasic OCP
- When to stop?

Patient #2

- 54 yo woman
- LMP 2 years ago
- 10 hot flashes per day
- 3 night sweats per night
- Waking more than she used to

Patient #2 How to manage?

- She is fully menopausal and incredibly symptomatic
- Start E + P in a patch (Combipatch) or E in a 0.5 mg/day patch and prometrium 100 mg at night
  - Could also consider LNS IUD
- Give her sleep hygiene recs
- See her back in 6-8 weeks

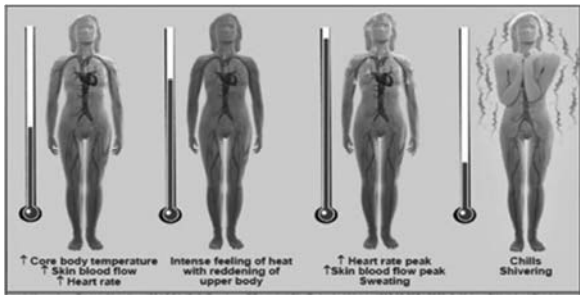
Vasomotor Symptoms

Incidence of Vasomotor Symptoms

- 454 US women in the Massachusetts Women's Health Study
- 75% experienced hot flashes in menopause
- Worse/prolonged
  - If menopause is surgical
  - If transition is early/premature

Avis NE, Women's Health 1997;3:103-120

Hot flash physiology



Natural History of Vasomotor Symptoms

- 30-50% of women note spontaneous improvement in 1-2 years
- 85-90% experience resolution within 4 to 5 years
- 10-15% of women will continue to have symptoms many years after menopause

NAMS Position Statement

- HT is the gold standard for relief of vasomotor symptoms
  - ET
  - E+PT
  - PT
- Use the **lowest dose that gives relief** and periodically reevaluate
- SSRIs/SNRIs best alternative; gabapentin third-line

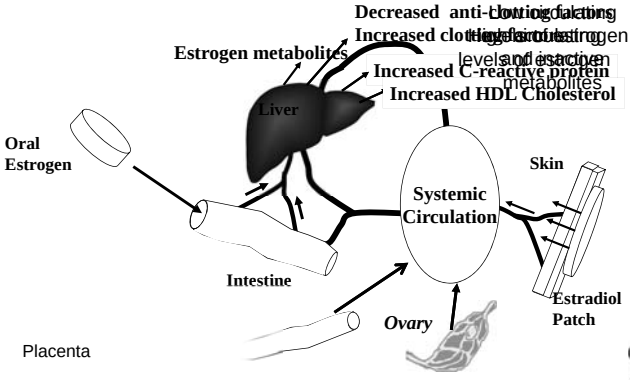
Type, dose, regimen, duration

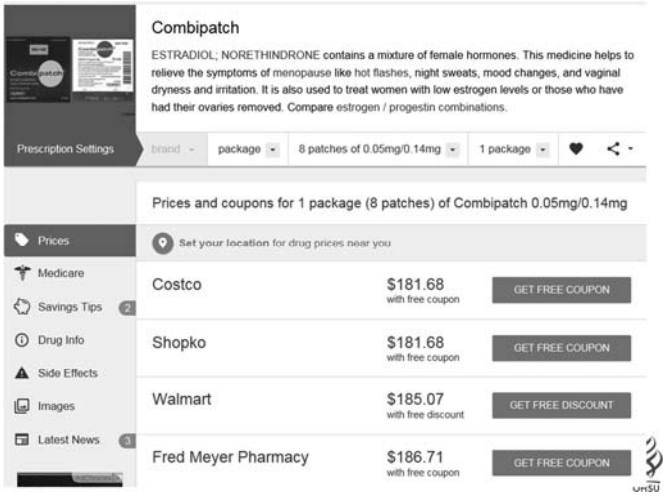
- Women with a uterus need P
  - Prometrium 100 mg q hs
  - Mirena or Skyla IUD
- Transdermal may decrease some risks
  - No RCT data, observational only
- Decisions about continuation must be individualized

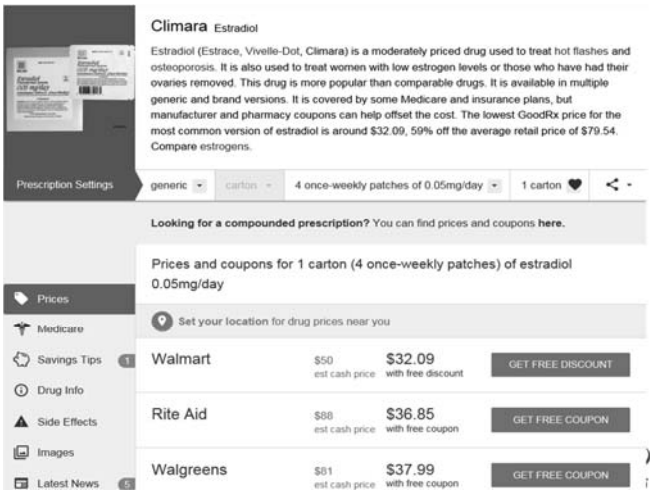
Oral vs. transdermal estrogen therapy and thromboembolic complications

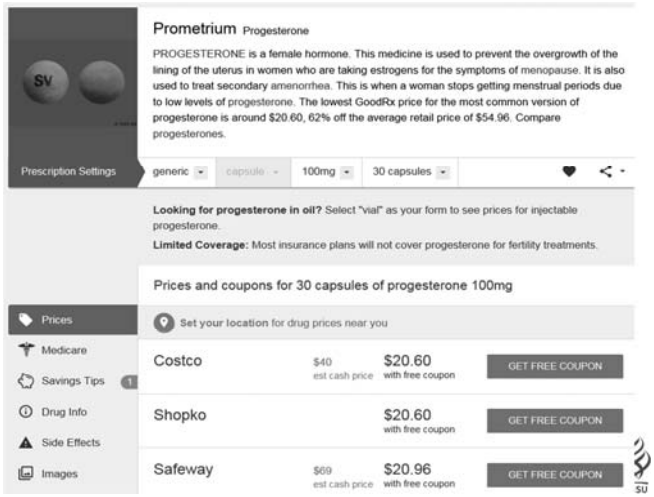
Study Publication	Oral Estrogen	Transdermal Estrogen
	Odds Ratios (95% Confidence Intervals)	
Scarabin, et al. Lancet, 2003, 362(9382): p. 428-32.	3.5 (1.8-6.8)	0.9 (0.5-1.6)
Canonico, et al. Circulation, 2007,115: 840-845	4.2 (1.5-11.6)	0.9 (0.4-2.1)

First Pass Hepatic Effects of Estrogens Taken by Mouth Mimic Pregnancy







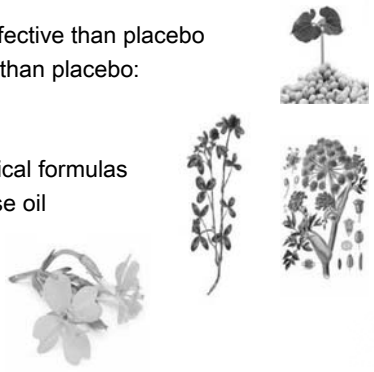


Practice Pearl : dosing gabapentin for vasomotor symptoms

	Morning	Afternoon	Evening
First 7 days			100 mg
Next 7 days	100 mg		100 mg
Next 7 days	100 mg	100 mg	100 mg
Next 7 days	100 mg	100 mg	200 mg
Next 7 days	200 mg	100 mg	200 mg
etc	Etc up to 300 mg	Etc up to 300 mg	Etc up to 300 mg

What about herbs/botanicals?

- Soy a little more effective than placebo
- Not more effective than placebo:
  - Red clover
  - Dong quai
  - Women's botanical formulas
  - Evening primrose oil
  - Black cohosh



Patient #3 how to evaluate?

- 35 year old woman
- No period for 10 months

Patient #3 how to manage?

- 35 year old woman
- No period for 10 months
- HCG neg
- TSH, PRL normal
- FSH 59, Estradiol 12
- Neg P withdrawal bleed

Early menopause/POI

- Benefits outweigh risks
  - Bone
  - Heart
  - Cognition
  - VVA/GSM
  - Sexual function
  - Mood
- HT recommended at least until age of menopause
- Younger women may require higher doses

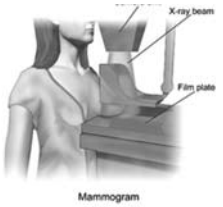
Patient #4 how to manage?

- 40 year old woman
- BRCA+
- Planning RRBSO

Family history of breast cancer

- HT doesn't alter risk for breast cancer in women with a family history
- This risk should be assessed when counseling women
- BRCA+ women who have undergone RRSO can be given HT until at least the age of menopause

Breast cancer



Mammogram

- HT's effect on risk of breast cancer is complex and conflicting
- May depend on
  - Type of HT, dose, duration of use
  - Regimen, route of administration
  - Individual characteristics

Breast cancer and WHI

- Increased risk of invasive breast cancer after 3-5 years of CEE + MPA
- No increased risk of breast cancer seen with 7 years of CEE alone
- Allows more flexibility in use of HT in women without a uterus
- Risk is greater from **sedentary lifestyle, obesity, or alcohol intake** than from estrogen

Survivors of endometrial cancer

- HT can be considered in women with early stage endometrial cancer surgically treated if other options ineffective
  - Especially if younger than age 51
- Non-hormonal therapies recommended for more advanced stages
- Low dose vaginal ET may be given for relief of GSM/VVA

Survivors of breast cancer

Survivors of breast cancer

- NO!
- Selected cases with compelling reasons may be discussed with medical oncologist
- After nonhormonal options have failed
- Local ET for GSM/VVA is an option
  - Try nonhormonal options first
- NOT if on aromatase inhibitors without consultation

Duration

- Risk/benefit balance (vasomotor sx, bone loss)
- Absolute risks that increase with age
  - CHD
  - Stroke
  - VTE
  - PE
  - Breast cancer
- No recommendation to automatically stop at age 65

Patient #5

- 59 yo African American woman
- Has been struggling with hot flashes for years
- T2DM
- On a statin and a BP med

NAMS MenoPro App incorporates the ASCVD risk calculator

MenoPro | NAMS

The app asks you

- Age?
- Less than 10 years past the onset of menopause?
- Hysterectomy?
- Ethnicity?
- Smoker?
- Treatment for HTN?
- Systolic BP?
- Diabetes?
- On cholesterol-lowering medication?
- Total cholesterol level?
- HDL?

Then you wait…

Results Page

- Gives the patient's CVD Risk Score over 10 years
- Gives you a list of every appropriate treatment option and dosages

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Patient #5

- "The CVD Risk Score is 13.9% (high risk) over 10 years"
- "Patients with CVD risk scores above 10% should avoid initiation of systemic hormone therapy but may be candidates for non-hormonal therapy"

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Patient #6

- 56 yo woman
- BMI 19.6
- Smoker
- Mother had a hip fracture

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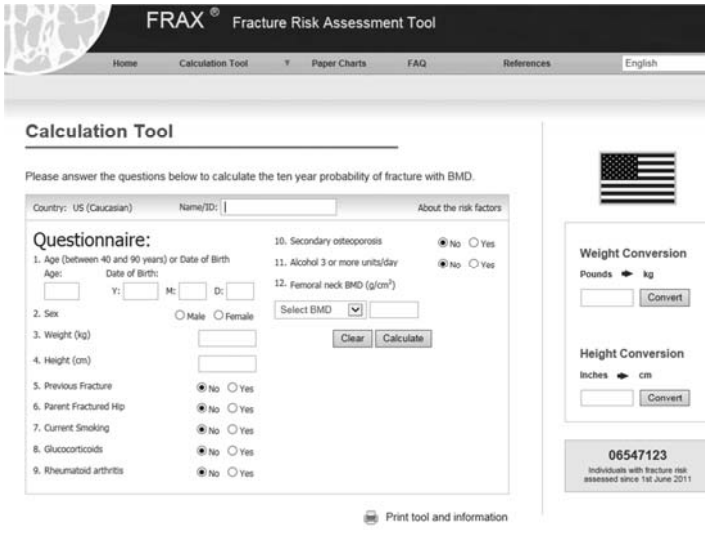
BMD testing recommendations

- All women age 65 and older
- Postmenopausal women younger than age 65 if FRAX score for 10-year risk of major fracture is ≥9.3% (average fracture risk for healthy women)
- Postmenopausal women with medical causes of bone loss
- Postmenopausal women with history of fragility fracture

Pfister AK *Ann Intern Med* 2011;155:275-6



Osteoporosis risk assessment

- Identify postmenopausal women at risk for fracture using FRAX
- Institute measures that reduce modifiable risk factors through dietary and lifestyle changes
- If indicated, prescribe pharmacologic therapy or refer for this treatment

When is drug therapy needed?

- History of vertebral, hip, fragility, or low-trauma fracture
- BMD values = osteoporosis (T score ≤ –2.5)
- 10-year FRAX risk of major osteoporotic fracture of at least 20% or hip fracture of at least 3%
- May consider estrogen for this purpose

NAMS *Menopause* 2010;17:25-54

HT and Fracture Prevention

- WHI was the first RCT evidence that HT reduced risk of fractures even in low risk women
- Average T scores of women in WHI
  - hip -0.94
  - spine -1.3
- Vertebral and radiologically-detected not included in global index

Patient #6

- 10 year risk of osteoporotic fracture = 11%
- 10 year risk of hip fracture = 1.2%
- Can consider HT because she is higher than average risk for healthy women

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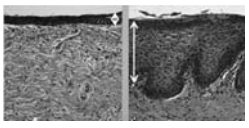
FDA-approved indications for HT



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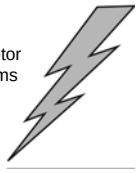
FDA-approved indications for HT

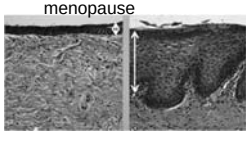
Vasomotor symptoms



Surgically or medically menopausal women

Treatment of women at high risk for osteoporosis

Genitourinary syndrome of menopause



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US Preventative Services Task Force 2017

Final Recommendation Statement

Hormone Therapy in Postmenopausal Women: Primary Prevention of Chronic Conditions

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Postmenopausal women	The USPSTF recommends against the use of combined estrogen and progestin for the primary prevention of chronic conditions in postmenopausal women.	D
Postmenopausal women who have had a hysterectomy	The USPSTF recommends against the use of estrogen alone for the primary prevention of chronic conditions in postmenopausal women who have had a hysterectomy.	D

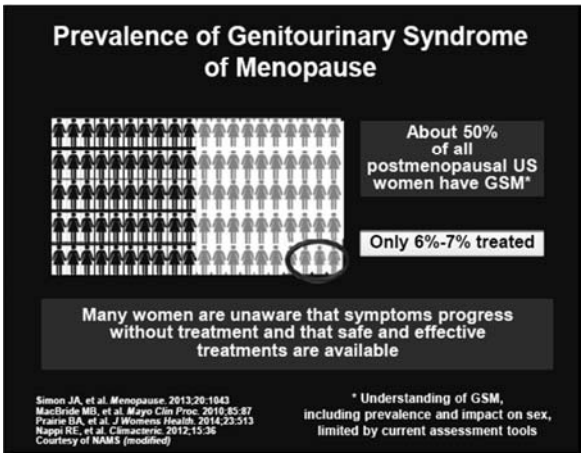
Grade D = evidence of no net benefit or harms outweigh benefits

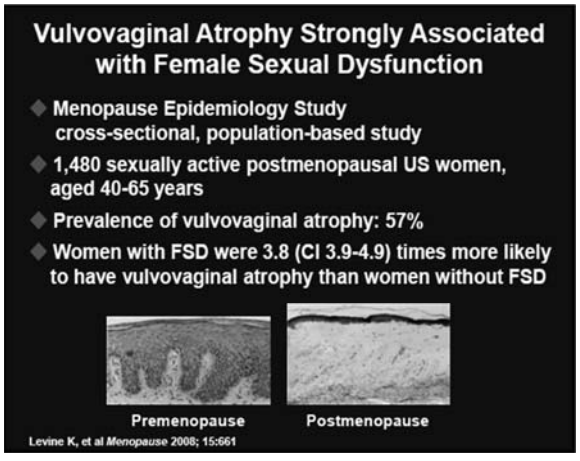
Patient #7

- 59 year old woman
  - No hot flashes
  - Increasing dyspareunia

Genitourinary Syndrome of Menopause

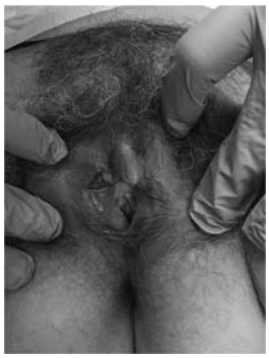
- **SYMPTOMS**
  - Vulvar/vaginal dryness
  - Decreased lubrication with sex
  - Discomfort or pain with sex
  - Bleeding after sex
  - Decreased arousal, orgasm, desire
  - Irritation, burning, or itching of vulva or vagina
  - Painful urination
  - Urinary frequency/urgency
- **SIGNS**
  - Decreased moisture
  - Decreased elasticity
  - Labia minora get thinner
  - Pale vaginal tissue
  - Loss of vaginal folds
  - Tissue fragility/splitting





Diagnosis of GSM

- Look for it in peri or post menopausal women
- Thin thin thin
- Dry dry dry
- Ask about symptoms



NAMS guidelines for GSM

- Start with OTC lubricants and moisturizers
- Lubricants with sexual activity
  - Coconut oil
  - Silicone
- Moisturizers for weekly maintenance
- If no improvement after 3 months, move to pharmacologic options

Vaginal Moisturizers

FDA-approved estradiol treatments

- Topical vaginal cream (Estrace)
  - ½ gm on fingertip and/or 1 gm in vagina nightly x 2 weeks then 2x week
- Vagifem tablets or Estring inserted in the vagina
- Estrogen softgel approved June 2018 ("more elegant delivery system")

Safety of local E therapy

- Reassuring when serum levels are measured
  Serum levels: E cream > E tablet > E ring
  All within menopause levels
- Reassuring when endometrial stripes are ck'd
- We now have 7-year follow up
- Breast cancer survivors need to know what is safe
- Women on aromatase inhibitors with vaginal E add-back had higher serum E levels (still menopausal range)

VAGIFEM 10mcg
estradiol vaginal inserts

SCARY PACKAGE LABELLING!

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VAGIFEM® safely and effectively. See full prescribing information for VAGIFEM®.

Vagifem® (estradiol vaginal inserts)

Initial U.S. Approval: 1999

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.2)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

RECENT MAJOR CHANGES

- Warnings and Precautions, Malignant Neoplasms (5.3) 11/2017

INDICATIONS AND USAGE

- Vagifem® is an estrogen (estradiol) indicated for the treatment of atrophic vaginitis due to menopause (1.1).

DOSAGE AND ADMINISTRATION

Vagifem® should be administered intravaginally:

- 1 insert daily for 2 weeks, followed by 1 insert twice weekly (for example, Tuesday and Friday) (2.1)

DOSAGE FORMS AND STRENGTHS

- Vagifem® 10 mcg insert. One vaginal insert contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol (3)
- Vagifem® 25 mcg insert. One vaginal insert contains 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active DVT, PE, or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.2)
- Known anaphylactic reaction or angioedema to Vagifem®
- Known liver impairment or disease (4, 5.11)
- Known protein C, protein S, or antithrombin deficient, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- The Vagifem® applicator may cause vaginal abrasion (5.17)
- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

ADVERSE REACTIONS

In prospective, randomized, placebo-controlled, double-blind studies the most common adverse reactions (incidence ≥5 percent) were upper respiratory tract infection, headache, abdominal pain, back pain, genital pruritus, moniliasis, vulvovaginal mycotic infection and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-824-4336 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

USE IN SPECIFIC POPULATIONS

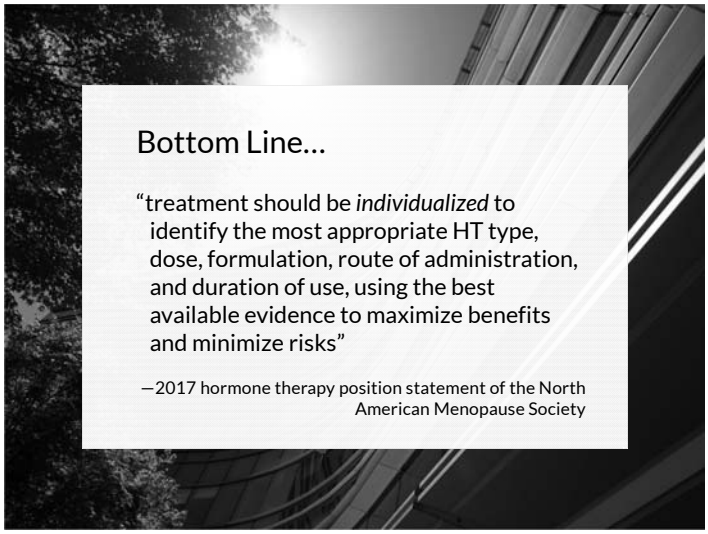
- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2017

Choices of local therapy

- User abuse is less likely with vaginal tablets or vaginal ring – temptation to use lots of cream
  - Med oncs are happier with tablet or ring than cream
- Breast pain signifies systemic exposure
  Incidence = <3% with semi-weekly use



Bottom Line…

"treatment should be *individualized* to identify the most appropriate HT type, dose, formulation, route of administration, and duration of use, using the best available evidence to maximize benefits and minimize risks"

—2017 hormone therapy position statement of the North American Menopause Society

Menopausal Zest

- In a Gallup survey of 752 women, in the majority of women these areas were better or stable:
  - role at work
  - family life
  - partner/sexual relationship
  - friendships
  - self-fulfillment
  - and physical health.

Utian WH Menopause 1999;6:122-8

OHSU

Thank You

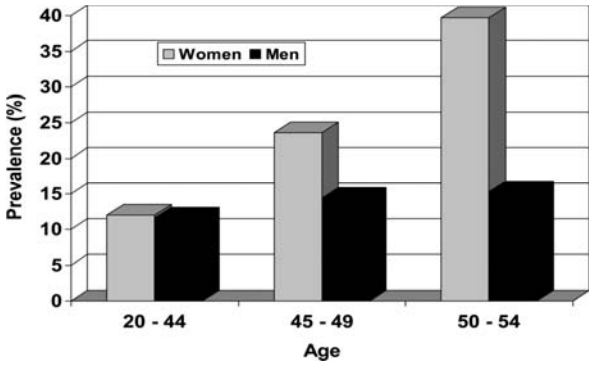
Extra Credit: Clinical Approach to the Midlife Woman

- Sleep disturbances
- Cognition
- Mood
- Urinary symptoms

Sleep

- Midlife women
  - sleep less
  - have more frequent insomnia
  - are more likely to use prescription sleep aids
- Hot flushes actually happen AFTER awakening

Age-related sex differences in self-reported sleep problems



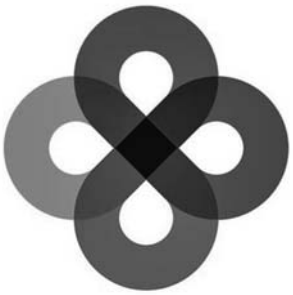
Cirignotta et al. Insomnia: an epidemiological survey. Clin Neuropharm 1985

Causes of Disturbed Sleep in Menopause

Sleep

- Decisions about treatment (behavioral or drug tx) depend on
  - severity of disturbance
  - context of sleep problem
  - daytime consequences

Mood, sleep, cognition…



Mood, Sleep, Cognition

- Women are 2-4X more likely to experience a major depressive episode in peri- or early-post menopause
  - independent of hx of depression, upsetting life events, and hot flashes
- 37% of women ages 40-55 report difficulty sleeping
- Brain fog is common as we age, starting around 50 yo
  - difficult to sort out the role of estrogen

Cognition

- Midlife women should be counseled that memory and concentration problems are probably not related to menopause
  - Normal aging
  - Mood
  - Stress
  - Other life circumstances
- Sleep is essential

Mood

- The most predictive factor for depression at midlife is a history of depression
- Fluctuating hormone levels don't help!
- Women with a history of PMS, significant stress, sexual dysfunction, physical inactivity, or hot flashes are more vulnerable
- Sleep is essential

What about HT?

- Mood, sleep, cognition *may* improve with HT
- Specific treatment appropriate for
  - **Adverse mood** (15-20%)
    - r/o moderate to severe depression
  - **Persistent poor sleep** (30-60%): hypnotics, CBT
  - **Cognitive issues**: research into ADHD meds/low dose CNS stimulants

Soares Menopause 2014; 21:198; Kravitz Ob Gyn Clin North Am 2011; 38: 567; Epperson Menopause 2011; 18:542; Psychpharmacology 2015; 232:3091

Urinary symptoms

- Urinary complaints are common in midlife women but no link to menopause-related estrogen loss has been identified
- Over 50% of women >age 50 with urinary incontinence, also report symptoms of overactive bladder (OAB)
- Mild incontinence in early perimenopause tends to decline in the first 5 years after menopause

Urinary symptoms

- Weight loss for overweight women is effective
- Kegel exercises can cure more than 50% of cases of stress incontinence when performed regularly
- Several medications are approved for OAB

Iron: TOO LITTLE OR TOO MUCH!

Joseph J. Shatzel, MD
Catherine Murphree, MD

Disclosures

- Dr Shatzel: Has received consulting fees from Aronora Inc.
- Dr. Murphree: None

Quick Iron Overview

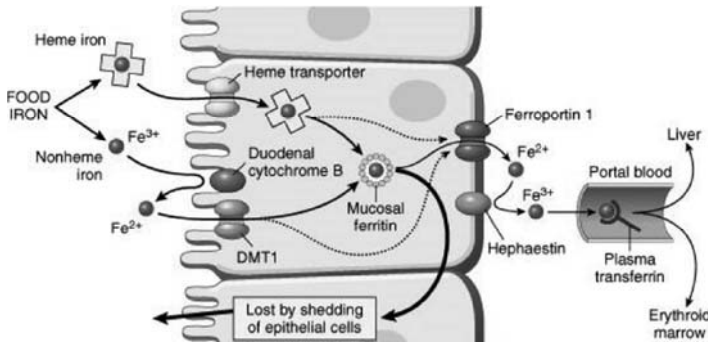
- What is the purpose of iron?
- Hemoglobin synthesis
- In body- exists in complex forms
- Iron -> intestinal enterocytes/ reticuloendothelial macrohpages -> transferrin -> taken to mitochondria

A few key players

- Transferrin
- Ferritin
- Ferroportin
- Hepcidin
- BMP- bone morphogenetic proteins

Iron Homeostasis

- Feedback mechanism?
- Hepcidin- secreted by liver- main regulator of iron homeostasis – hormone- produced hepatocytes
- How does it work?
- What regulates hepcidin?
- Why does we care? Iron- toxic- lead to generation of ROS



Diagnosis and Treatment of Adult Iron Deficiency Anemia

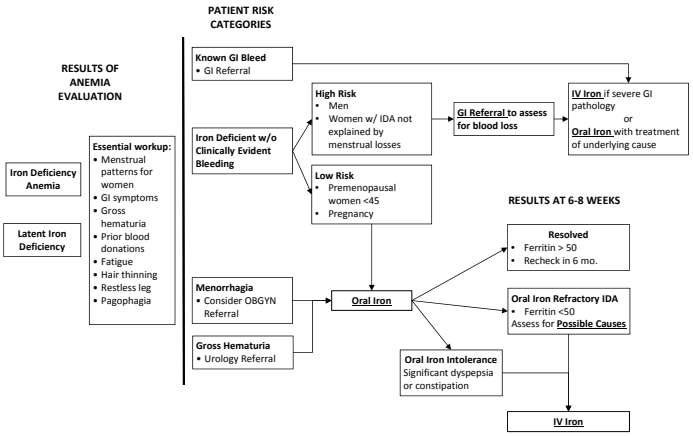
Updated:

1. Interpretation of Iron Studies
2. Diagnosis & Management of Adult IDA
3. Renal Disease IDA Treatment Guidelines
4. Microcytic Anemias of Adequate Iron Stores
5. Evaluating for GI Causes of IDA
6. Oral Iron Treatment
7. IV Iron Treatment
8. Special Scenarios

Microcytic Anemia of Adequate Iron Stores

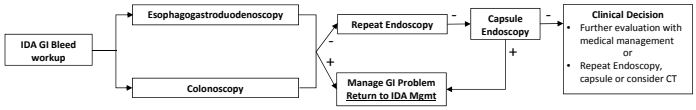
Cause	Characteristics	Diagnostic Workup	Treatment Recommendations
Anemia of Chronic Disease	Associated with infectious, inflammatory, or neoplastic disease	Diagnosis of exclusion. EPO levels often low or normal relative to degree of anemia.	• Correction of underlying disorder if possible **Severe** • Transfusion • Exogenous EPO or ESA
Iron Refractory Iron Deficiency Anemia (IRIDA)	Hereditary recessive anemia that may be recognized in adulthood. Suspect if: • Normal CRP (distinguish from Anemia of CD)	Rule out other causes of iron deficiency refractory to iron therapy. Genetic testing for biallelic mutation in TMPRSS6	• Very few patients respond to oral iron. • Repeated IV iron may improve Hb ***Attempts to correct to reference range risks putting patient into iron overload***

Management of Iron Deficiency



Evaluation for GI Causes of IDA

Evaluation for GI Bleed with IDA



Adapted from Evaluation of Occult Gastrointestinal Bleeding. Am Fam Physician. 2013;87(6):430-436

Possible Causes of Oral Refractory IDA

GI Pathology	Laboratory Screening
Helicobacter Pylori	Urea breath test or stool antigen assay.
Celiac Disease	Serologic testing: Total IgA and Anti-tissue transglutaminase antibody (TTGA) testing if low risk, Duodenal Biopsy if high risk
Chronic Autoimmune Gastritis	Serum gastrin and anti-parietal or anti-intrinsic-factor antibody with gastroscopic biopsy (recommended)

Oral Iron Treatment

Any preparation > 18mg of elemental iron is sufficient:

Oral Iron Formulations [6]	Dose
Ferrous Sulfate	325 mg alternate daily ingestion
Ferrous Sulfate anyhydrous	200 mg alternate daily ingestion
Ferrous Gluconate	325 mg alternate daily ingestion
Ferrous Fumarate	325 mg alternate daily ingestion
Polysaccharide iron complex	50 mg alternate daily ingestion
Heme iron polypeptide	24 mg alternate daily ingestion
Carbonyl iron	45 mg (Feosol) alternate daily ingestion 66 mg (Ircon) alternate daily ingestion
Ferric citrate	210 mg alternate daily ingestion
Ferrous ascorbate	200 mg alternate daily ingestion
Ferrous succinate	200 mg alternate daily ingestion

Other important considerations:
Take with 500mg of ascorbic acid; Avoid administration with tea or coffee,
Providing iron supplements on alternate days and in single doses optimizes iron absorption and might be a preferable dosing regimen*

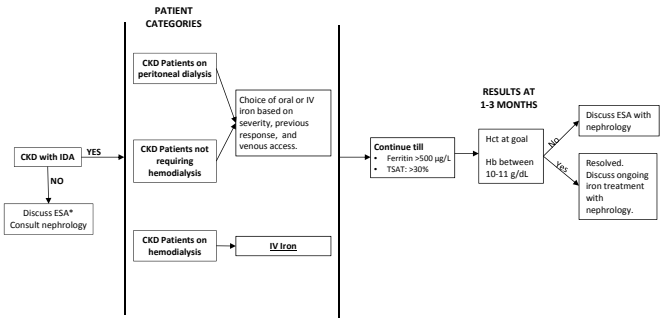
IV Iron Treatment

Trade Name	INFeD-US Cosmofer	Feraheme	Injectafer, US Ferinject	Monofer-Europe Only	Venofer*	Ferrlecit*
Generic Name	LMW iron dextran	Ferumoxytol	FCM	Iron isomaltoside	Iron sucrose	Sodium ferric gluconate
Manufacturer	Allergan/Watson pharma	AMAG Pharmaceuticals	**Vifor Pharma**	Pharmacosmos	American Regent Inc	Sanofi Aventis Inc
Carbohydrate	Low-molecular-weight iron dextran	Ferumoxytol	Carboxymaltose	Isomaltoside	Sucrose	Gluconate
Total dose infusion (TDI)	Yes	No	Yes	Yes	No	No
Test dose required	Yes	No	No	No	No	No
Approved dose	100 mg per dose	510 mg over 15 min	750 mg over 15 min	20 mg/kg (1000 mg if >66 kg)		
Recommended dose	1000 mg	510 mg x 2	750 mg x 2	1000 mg	200-300 mg	125-187.5 mg
Infusion time	1 hour	15 min	15 min	15 min	15 min	1 hour
Black box warning	Yes	Yes	Yes*	NA	No	No
Pregnancy Category	C	C	C	Not listed	B	B

Avoid treatment with IV iron in patients with active systemic infections. [1]
Frumoxytol is clinically superior to FCM **

Adapted from Single-dose intravenous iron for iron deficiency: a new paradigm. Hematology Am Soc Hematol Educ Program. 2016;2016(1):57-66.

Renal Disease IDA Treatment Guidelines



Adapted from *Chapter 2: Use of iron to treat anemia in CKD. Kidney Int Suppl (2011). 2012;2(4):292-298.*

*Do not initiate Erythropoietin Stimulating Agent (ESA) in the presence of absolute iron deficiency (ferritin <30µg/L) till it is corrected & anemia persists. [4]
When considering IV iron for people not receiving in-center hemodialysis, consider **high dose, low frequency (HD/LF) IV iron. [4]

Table of Contents

Special Scenarios

Special Scenario	Treatment
Pregnancy (3rd trimester)	IV Ferrous Carboxymaltose
Heart Failure (Ferritin <100µg/L, or ferritin 100-300µg/L AND Tsat <20%)	IV Ferric Carboxymaltose up to two infusions of 1000mg of iron (more if anemia persists) is recommended regardless of hemoglobin values. Meta-analysis outcomes are suggestive of reduced CV hospitalizations, improved NYHA status and HF symptoms, and all-cause mortality. Use of oral iron supplementation in patients with HFrEF not supported

What to do with a high ferritin?

- Transferrin saturation
- LFTs, RFTs, CBC, inflammatory markers (ESR, CRP)
- Blood glucose
- Lipids
- When should measure?

Causes of elevated ferritin, w/out iron overload

- 90% of patients with hyperferritinemia will not have iron overload!
- Acute/chronic inflammation
- Hepatic injury- hepatitis, NASH
- Infection
- Alcohol
- What else?

Why are we even worried about Iron Overload?

- ROS
- Labile plasma iron- produces ROS through Haber-Weiss Fenton reactions
- Alters mitochondrial function
- Hepatocytes, pancreatic cells, cardiac myocytes prone to taking up NTBI leading to fibrosis, cirrhosis, HCC, diabetes, infiltrative heart failure

If not previous then..

Primary Iron overload

- HFE hemochromatosis
- Non HFE hemochromatosis

Secondary Iron overload

- Repeat blood transfusions (HSCT, sickle cell)
- Repeat IV iron infusions (renal failure, cancer)
- Thalassemia , hemolytic anemias, sideroblastic anemias, MDS, aplastic anemia

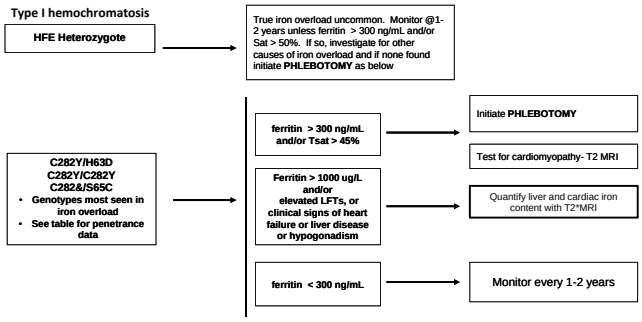
HFE Hemochromatosis

- 90% C282Y/C282 homozygosity- extremely high prevalence! Low penetrance! (28% males, 1.2% females)
- Rare iron overload seen in C282Y/H63D mutations
- S65C other mutation seen

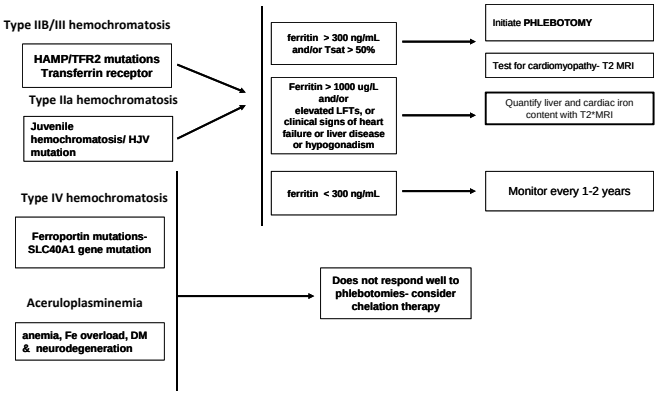
Non-HFE Hemochromatosis

- HJV
- HAMP
- TfR2
- SLC40A1
- Extremely rare – less than 5%

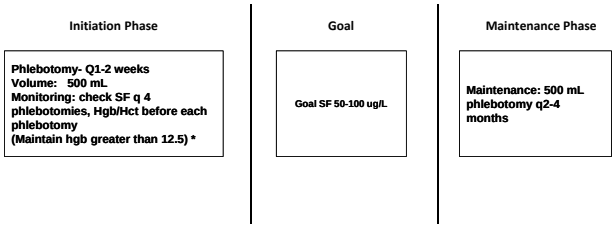
Management of Hemochromatosis



Management of Non HFE-Hemochromatosis



Phlebotomy



(Very rarely, chelation therapy may be required in anemic patients who cannot tolerate phlebotomy) *

Hemochromatosis Penetrance

Genotype	Male Penetrance	Female Penetrance
C282Y/C282Y	Evidence suggests 28% of ***MALE*** homozygotes have documented iron overload clinical disease	Evidence suggests 1.2% of ***FEMALES*** have documented iron overload clinical disease
C282Y/H63D	< 1.5%	<1.5%

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Shared Decision Making for Breast Cancer

April 11, 2019

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Disclosures/Conflict of Interest

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Acknowledgements

- Heidi D. Nelson MD, MPH
- Karen B. Eden, PhD

Session Objectives

- Review current breast cancer screening clinical guidelines and coverage recommendations.
- Understand current evidence of the benefits and harms of breast cancer screening.
- Understand shared decision making for breast cancer.
- Understand how to implement shared decision making for breast cancer.

U.S. Preventive Services Task Force

- An *independent, non-governmental* panel of experts in primary care and prevention.
- Develops recommendations for clinical preventive services for primary care clinicians.
- Based on rigorous review of existing peer-reviewed evidence.
- Preventive services include:
  - Screening tests
  - Counseling
  - Preventive medications

U.S. Preventive Services Task Force

Grade	Suggestions for Practice
A	Offer or provide this service
B	Offer or provide this service
C	Offer or provide this service for selected patients depending on individual circumstances.
D	Discourage the use of this service.
I	Read the clinical considerations of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

A and B recommendations are covered services under the ACA

Case Example

A 40-year-old G2P2 female presents for a well woman preventive visit. She feels well and takes no medications. She lives with her husband and two children, ages 7 and 11. Before the birth of her first child, she took COC's for 6 years. She breast-fed each of her children for ~1 year. Current contraception method is levonorgestrel IUD. She has a healthy diet, exercises 2-3x/week, does not smoke, and drinks ~ four glasses of wine/ week. +FH includes prostate cancer in her father at 75, and hypertension in her mother at 60. No FH of colon, lung, or breast cancer. Complete physical exam is normal, including a clinical breast examination. She asks about recommendations for breast cancer screening.

Question:

Do you recommend breast cancer screening?

a) Yes, start annual screening mammography at age 40.
b) No, wait to initiate screening mammography until age 50.
c) Offer shared decision making to help the patient decide whether to begin screening.
d) I am confused about breast cancer screening guidelines.

Breast Cancer Clinical Guidelines

U.S. Preventive Services Task Force 2016

Age, *y*	Recommendation
40 to 49	Individual decision (C)
50 to 59	Screen every 2 years (B)
60 to 69	
70 to 74	
75 and older	Individual decision (Insufficient)

Insufficient Evidence

- Digital breast tomosynthesis (DBT) as a primary screening method.
- Adjunctive screening in women identified to have dense breasts on an otherwise negative screening mammogram using breast ultrasonography, magnetic resonance imaging, DBT, or other methods.

Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164:279–296. doi: 10.7326/M15-2886

U.S. Preventive Services Task Force
www.uspreventiveservicestaskforce.org

Women's Preventive Services Initiative
www.womenspreventivehealth.org

Affordable Care Act
www.healthcare.gov

WPSI
Women's Preventive Services Initiative

- Supported by HRSA, led by ACOG since 2016.
- National collaborative of women's health professional societies to develop, review, update, and disseminate recommendations for women's preventive health services.
- Targets preventive health service *gaps*.
- Recommendations used to guide clinical practice and coverage of services for the ACA and other stakeholders.
- http://www.womenspreventivehealth.org

Current Coverage Recommendations

Women's Preventive Services Initiative 12/2016

Average-risk women

- Initiate mammography screening no earlier than age 40 and no later than age 50.
- Screening mammography should occur at least biennially and as frequently as annually.
- Screening should continue through at least age 74 and age alone should not be the basis to discontinue screening.

Current Coverage Recommendations

Women's Preventive Services Initiative 12/2016

- Decisions regarding when to initiate screening, how often to screen, and when to stop screening should be based on a periodic ***shared decision-making process*** involving the woman and her health care provider.
- The ***shared decision-making process*** assists women in making an informed decision and includes,
  - Discussion about the benefits and harms of screening
  - Assessment of the woman's values and preferences
  - Consideration of factors such as life expectancy, comorbidities, and health status.

Evidence
Based on IOM
Standards for
Systematic Reviews

CLINICAL
PRACTICE
GUIDELINES
WE CAN
TRUST

Practice Guideline
Based on IOM
Standards for Clinical
Guidelines
USPSTF
WPSI

ACA Mandate*

Insurance
Private & Public

*ACA—no co-pay or deductible affecting 60 million women in the U.S.

Evidence Based on Systematic Reviews

- Summary of available scientific evidence.
- Studies are collected, evaluated, and synthesized using an established methodology.
- Provides accurate, independent information of benefits and harms of prevention interventions for specific populations.
- Defines sources, type, strengths, and limitations of evidence.
- Avoids bias in finding, selecting, or analyzing evidence.

Evidence Review
Synthesizes the Body of Research

- Quantitative meta-analysis.
- Qualitative analysis.

Evidence
Defines Screening Target Population

Women age 40 and older → ***Screening Pool***
Average-risk women with no previous or current breast abnormalities

→ ***Not in Screening Pool***
- Current physical finding
- Previous breast cancer or other breast abnormality (DCIS, LCIS, ADH, ALH)
- BRCA deleterious mutation
- Strong family history (>15% risk)
- Familial cancer syndromes
- Extensive chest radiation

Evidence
Considers the Hierarchy of Evidence (Risk of Bias)

Least

Susceptible to Bias

Randomized controlled trial

Nonrandomized controlled trial

Cohort study

Case-control study

Before-after study, intervention series, case series, case reports

Most

Evidence
Considers Benefits and Harms

Possible Benefits	**Possible Harms**
Breast cancer mortality	False +/- results and biopsies
All-cause mortality	Over diagnosis
Advanced breast cancer	Anxiety, distress, pain
Treatment	Radiation exposure

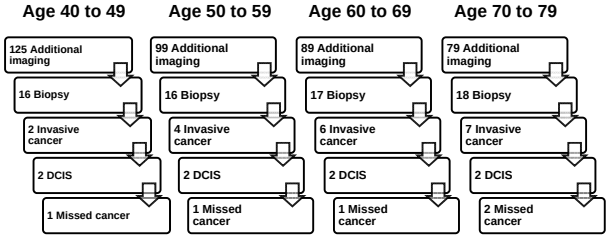
Mammography

Effectiveness and Adverse Effects of Breast Cancer Screening

2016 USPSTF Review of Evidence

Screening Outcomes

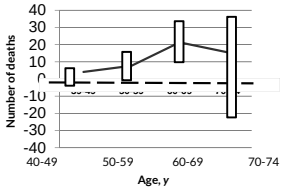
For Every 1,000 Women Who Have a Screening Mammogram



Nelson HD, et al. *Ann Intern Med*. 2016;164:256-267.

Breast Cancer Mortality

Deaths Prevented by Screening
10,000 over 10 years based on meta-analysis of 8 RCTs



Age, *y*	Number of deaths (95% CI)
40-49	3 (0 to 9)
50-59	8 (2 to 17)
60-69	21 (11 to 32)
70-74	13 (0 to 32)

Nelson HD, et al. *Ann Intern Med*. 2016;164:244-255

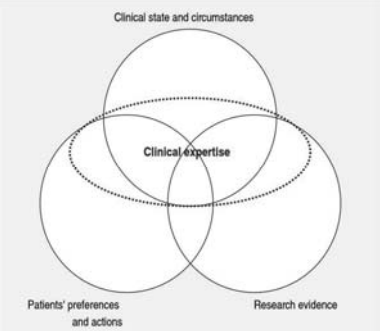
Summary of Benefits

- Breast cancer mortality reduction with screening:
  - Age 50 to 69 in RCTs and observational studies.
  - No differences for 40 to 49 in RCTs, limited observational data.
  - Limited data for age 70 and older.
- All-cause mortality was not reduced at any age with screening in RCTs.
- Advanced breast cancer outcomes were only reduced with screening for age 50 and older.

Summary of Harms

- False-positive results are common, especially among younger women.
- Cumulative false-positive rates are higher with annual screening.
- Women with false-positives have more anxiety and distress.
- Biopsy results may be inaccurate.
- Many women experience pain during mammography; some do not return for screening.

Evidence Does Not Make Decisions, People Do



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Shared Decision Making: a Definition

Integrative process between patient and clinician:

- Engages the patient in decision-making.
- Provides patient with information about alternative treatments.
- Facilitates the incorporation of patient preferences and values into the medical plan.

Slide from Michael Barry, MD, IMDF President

Charles C, *Soc Sci Med* 1997; 44:681.

When Do Preferences Really Matter?

Intervention	Description
Beneficial	Established benefit
Likely to be beneficial	Effectiveness is less well established
Trade off between benefits and harms	Clinicians and patients should weigh benefits and harms
Unknown effectiveness	Insufficient data
Unlikely to be beneficial	Likely to be ineffective or perhaps, harmful
Likely to be ineffective or harmful	Ineffective or associated with harm

Adapted from Clinical Evidence, BJM. http://clinicalevidence.bmj.com/ceweb/about/guide.jsp.

Why Use Shared Decision Making for Breast Cancer Screening?

- The age to start screening and the interval between screenings often depend on individualized decision-making.
- Decision aids help patients understand risk estimates and talk about them with a provider.

Decision Aids Can Help with Shared Decision Making

- Provide information about options.
- Give a common language for all.
- Give a safe way to set priorities for a decision or identify preferences.
- And by providing structured guidance for a shared discussion.

Which Skills do Clinicians Most Need to Improve?

- Assess patients' values.
- Ask about patients preferred role in decisions.
- Screen for decisional conflict.
- Assess support or undue pressure on patient.
- Increase patients' involvement in decision making.

Adapted from Légaré, Canadian Family Physician, April, 2006.

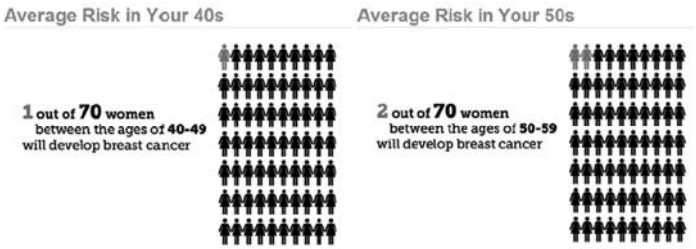
Breast Cancer Screening Values

- Are you willing to undergo interventions to detect breast cancer early?
- Do you see mammograms as painful or inconvenient?
- Do you want a recommendation about mammograms from your provider?
- How concerned are you about your individual breast cancer risk?

Differences in Screening Recommendations

Experts agree that women of average risk should be getting regular mammograms by age 50, but they don't agree about starting at 40

Explaining Risk: Numbers and Graphics



Mammography Screening Decision Aid

Provides Information on Risk and Types of Cancer

OHSU Patient Handout

OHSU HEALTH

Breast Cancer Screening

Why screen for breast cancer?

Breast cancer is the second most common cancer and the second leading cause of cancer death in women in the United States. Screening means checking a woman's breasts for cancer before she has any symptoms. A mammogram is a screening tool to find breast cancer early so treatment can be more effective in reducing deaths and disability from breast cancer.

Am I at average risk for breast cancer?

Routine screening is intended for women who are not at increased risk for breast cancer. If you have any of the following, you may have an increased risk and you should talk with your provider:

- Current breast pain, lump, or skin changes
- Personal history of breast cancer or breast abnormality
- One or more relatives with breast cancer
- A genetic mutation associated with increased risk for breast cancer (e.g., BRCA)
- Cancer or genetic syndrome that runs in your family
- History of radiation therapy to your chest before age 30

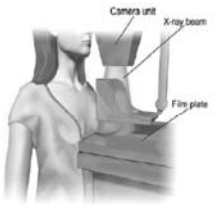
Patient centered language

When should I start screening? How often should I be checked?

Beginning at age 40, we encourage you to speak with your OHSU provider about whether starting screening mammography is appropriate for you. Although average risk women can begin routine screening at age 50, some may choose to begin at age 40. Like many decisions in health care, the decision about when to start and how often to screen for breast cancer is a personal one that considers your individual risk and your values and preferences. It is important to understand that the results of any screening test may indicate that further testing is recommended to determine whether or not cancer is present.

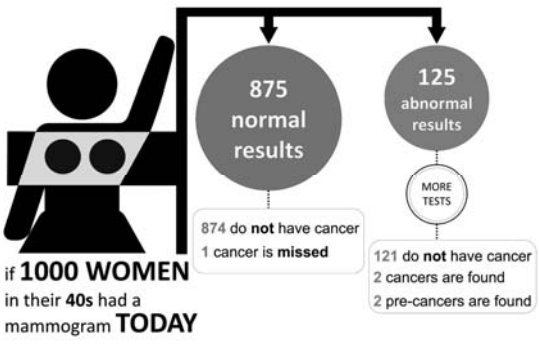
What is a mammogram? How is a mammogram done?

A mammogram is a tool to screen for breast cancer. It is an X-ray that provides a picture of breast tissue. Mammograms have much lower doses of radiation than usual x-rays. A woman stands in front of a special x-ray machine and a technologist places the breast on a platform. Another plate firmly presses the breast from above. The plate flattens the breast, holding it still while the x-ray is taken. The other breast is x-rayed in the same way. These steps are then repeated to take a side view of each breast. The technologist checks the four images to make sure the pictures do not need to be retaken. Keep in mind that the technologist cannot tell you the results of your mammogram because a radiologist needs to read the mammogram and create a report.



Mammogram, image courtesy of Blausen.com staff "Blausen Gallery 2014."

Clear messaging



Graphic courtesy of Karen Eden

Data from *Nelson HD, et al. 2016;*

Describes Benefits and Risks

What are the benefits of mammograms?

Mammograms cannot prevent cancer, but they are the best way to detect breast cancer early when it is easier to treat, when the cancer is small or before symptoms such as a lump are felt.

What are the risks of mammograms?

As with other screening tests, mammograms are not perfect. Each time a mammogram is done, there is a risk that the test:

- **May suggest additional imaging is recommended**, where more x-rays or an ultrasound are recommended to evaluate the breast tissue.
- **May miss breast cancer.** Normal breast tissue can hide cancer so it doesn't show up on the mammogram.
- **May show something that looks like a tumor when it is not one.** This can lead to anxiety and recommendations for additional testing, such as a breast biopsy, where a doctor will use a needle to remove tissue from the suspicious area to see if breast cancer is present.
- **Can find cancer that will never cause a problem.** For example, some breast cancers may grow so slowly that even without treatment these cancers may never affect a woman's health. We do not know ahead of time which cancers will grow slowly and which will be more aggressive.

Screening results for average-risk women

For every 1000 women who choose to get screened

OHSU

Clinical Documentation

- **Epic shared decision making "dot phrases"**

Patient was given breast cancer screening shared decision aid: FM_IMC SDE - DO NOT REUSE - MA MAMMO 349070

Yes, patient was given breast cancer screening shared decision aid
No, patient was not given breast cancer screening shared decision aid

If no, please provide reason: FM_IMC SDE - DO NOT REUSE - MAMMO REASON 349071

N/A
Patient already received screening & health maintenance updated
Patient declined screening & health maintenance updated

(For women, ages 40 to less then 50 years) I discussed options with the patient and came to a shared decision to start screening mammograms: FM_IMC SDE - DO NOT REUSE - PROVIDER MAMMO 349069

Yes, patient to start screening
No, patient will not start screening

OHSU

Questions?

cantor@ohsu.edu

Improving Cognitive Assessments in Dementia:

The Role of Primary Care

Cara Levin, MD

Emily Morgan, MD

Christopher Terndrup, MD

26th Annual Internal Medicine Review

Sentinel Hotel- Portland, OR

11 April 2019

Agenda

- Diagnosing Dementia in Primary Care Clinics
- Cognitive Assessments in Dementia
- Our Quality Improvement Project
- Conclusions and Next Steps
- Questions (and then lunch!)

Objectives

- Review the impact, diagnosis and management of dementia from a primary care perspective.
- Appreciate the importance of regular cognitive assessments in patients with dementia.
- Understand the utility of specific over non-specific codes when tracking dementia in primary care clinics.
- Describe a quality improvement approach to improving rates of cognitive assessments in an Internal Medicine Clinic.

Agenda

- **Diagnosing Dementia in Primary Care Clinics**
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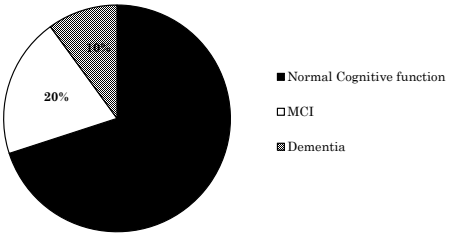
Prevalence of Dementia

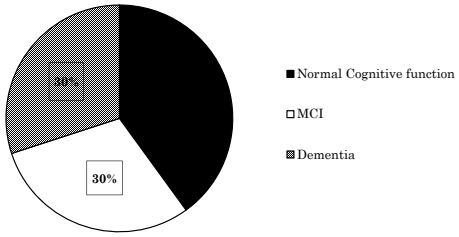
Total US Population Age **65+**



Langa KM, Larson EB, Crimmins EM, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. *JAMA Intern Med*. 2017;177(1):51-58.

Prevalence of Dementia

Total US Population Age **85+**



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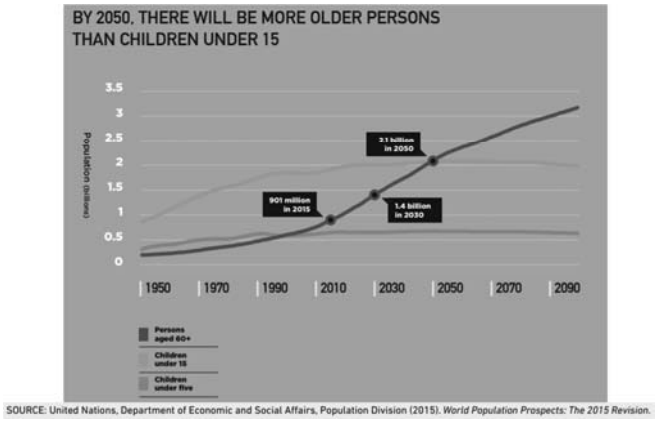


SOURCE: United Nations, Department of Economic and Social Affairs, Population Division (2015). *World Population Prospects: The 2015 Revision.*

Why is MCI important?

50% progress to dementia within 10 years

There are interventions that can potential prevent or slow the rate of conversion to dementia

- **Controlling vascular risk factors (OSA)**
- **Exercise (Tai chi)**
- **Diet (Mediterranean)**
- **Socialization (avoiding isolation)**

Missing the diagnosis

Alzheimer Disease International 2011 world report
- 2/3 of the world's people with dementia are undiagnosed

2015 WHO first Ministerial Conference for Dementia
- Call to focus on strengthening primary care as the key element to diagnosis

Primary Care Concerns

- Dementia cases are overlooked in 35-90% of primary care visits.
- No screening guidelines ⇨ Diagnosis requires trigger
- There are not enough geriatricians and neurologists to see all of the patients with cognitive complaints
- Benefit to early intervention including treatment of reversible causes of dementia

Valcour VG, Masaki KH, Curb J, Blanchette P. The Detection of Dementia in the Primary Care Setting. Arch Intern Med. 2000;160(19):2964-2968. doi:10.1001/archinte.160.19.2964.

Identification vs. Diagnosis

PCPs use >200 ICD10 diagnosis codes to identify cognitive impairment

Why does that matter???

- Management, counseling, and prognosis
- Research efforts
- Quality improvement

Physician Confidence in Dementia Care Skills Questionnaire*

For each item identified below, circle the number to the right that best corresponds to your **confidence level**:

BEFORE and AFTER today's training.

How confident are you in your ability to:		Confidence Scale Not at all ——> Extremely				
1. Screen patients for dementia?	Before training	1	2	3	4	5
	After training	1	2	3	4	5
2. Make a diagnosis of dementia?	Before training	1	2	3	4	5
	After training	1	2	3	4	5
3. Distinguish Alzheimer's Disease from other forms of dementia?	Before training	1	2	3	4	5
	After training	1	2	3	4	5
4. Understand the value and use of assessment instruments for cognition?	Before training	1	2	3	4	5
	After training	1	2	3	4	5
5. Understand the role of brain imaging in the diagnosis of dementia?	Before training	1	2	3	4	5
	After training	1	2	3	4	5
6. Provide initial treatment to patients with memory loss?	Before training	1	2	3	4	5
	After training	1	2	3	4	5
7. Use medications for memory loss?	Before training	1	2	3	4	5
	After training	1	2	3	4	5
8. Disclose and explain a diagnosis of dementia to a patient?	Before training	1	2	3	4	5
	After training	1	2	3	4	5

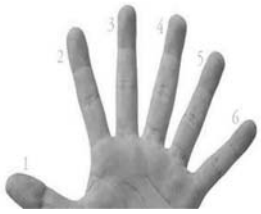
Obstacles to dementia diagnosis

Lowest provider confidence:

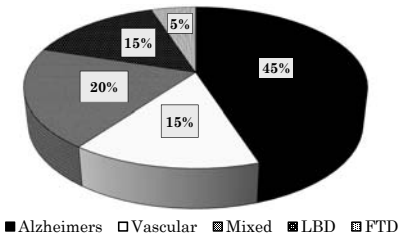
- Making a diagnosis
- DISTINGUISING BETWEEN AD AND OTHER DEMENTIAS
- Providing initial treatment
- Use of medications
- Deliver educational materials
- Refer to community resources

6 types of dementia

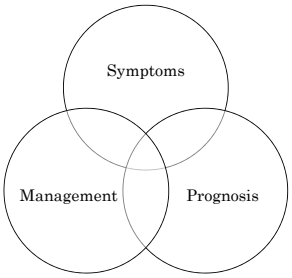
- **Alzheimer's**
- **Vascular**
- **Lewy Body**
- **Frontotemporal**
- **Alcohol related**
- **HIV Associated**



Dementia



Dementia
is not dementia
is not dementia



Agenda

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Quality Improvement in Dementia

- Dementia Work Measures Group (DWG)
- Dementia Management Desired Outcomes:
  - Preserving cognitive and functional abilities
  - Reducing the frequency, severity, and adverse effect of neuropsychiatric and behavioral symptoms
  - Sustaining the best achievable general health
  - Reducing risks to health and safety
  - Enhancing caregiver well-being, skill, and comfort with managing the individual with dementia in partnership with healthcare providers.

Odenheimer, G., Borson, S., Sanders, A. E., Swain-Eng, R. J., Kyomen, H. H., Tierney, S., ...&Johnson, J. (2013). Quality improvement in neurology: dementia management quality measures. *Neurology*, *81*(17), 1545-1549.

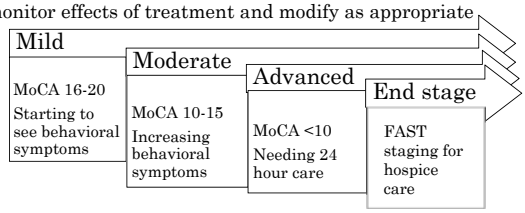
Dementia Management Quality Measures:

Table 1. Final 10 Dementia Measures

Measure	Description
1. Staging of dementia	Patients, regardless of age, with a diagnosis of dementia whose severity of dementia was classified as mild, moderate, or severe at least once within a 12-month period
2. Cognitive assessment	Patients, regardless of age, with a diagnosis of dementia for whom an assessment of cognition is performed and the results are reviewed at least once within a 12-month period
[illegible]	[illegible]
	status is performed and the results are reviewed at least once within a 12-month period
4. Neuropsychiatric symptom assessment	Patients, regardless of age, with a diagnosis of dementia and for whom an assessment of neuropsychiatric symptoms is performed and the results reviewed at least once in a 12-month period
5. Management of neuropsychiatric symptoms	Patients, regardless of age, with a diagnosis of dementia who have one or more neuropsychiatric symptoms who received or were recommended to receive an intervention for neuropsychiatric symptoms within a 12-month period
6. Screening for depressive symptoms	Patients, regardless of age, with a diagnosis of dementia who were screened for depressive symptoms within a 12-month period
7. Counseling regarding safety concerns	Patients, regardless of age, with a diagnosis of dementia, or their caregiver(s), who were counseled or referred for counseling regarding safety concerns within in a 12-month period
8. Counseling regarding risks of driving	Patients, regardless of age, with a diagnosis of dementia, or their caregiver(s), who were counseled regarding the risks of driving and the alternatives to driving at least once within a 12-month period
9. Palliative care counseling and advance care planning	Patients, regardless of age, with a diagnosis of dementia, or their caregiver(s), who received comprehensive counseling regarding ongoing palliation and symptom management and end of life decisions AND have an advance care plan or surrogate decision-maker in the medical record or documentation in the medical record that the patient did not wish or was not able to name a surrogate decision-maker or provide an advance care plan within 2 years of initial diagnosis or assumption of care
10. Caregiver education and support	Patients, regardless of age, with a diagnosis of dementia whose caregiver(s) were provided with education on dementia disease management and health behavior changes AND were referred to additional resources for support within a 12 month period

Annual Cognitive Assessments

- Cognitive deterioration can follow a different course depending on the type of dementia
- Regular assessments are key to good management of dementia
  - Identify goals of treatment
  - Develop a treatment plan
  - monitor effects of treatment and modify as appropriate



In the Clinic: 2/25/19

- Mrs. W is a 91 year old female who has been followed in our Geriatric Clinic who has a diagnosis of "dementia"; also has CKD and GERD. Comes to the clinic to meet her new provider (me) with her son and daughter-in-law.
- Medications: Donepezil 10 mg daily, Omeprazole 20 mg daily.
- Social history: Lives in independent living. Receives assistance with IADLs and some ADLs. Widowed.

During the Visit

- History/Medication Review
- Exam
- Cognitive Assessment

SLUMS Exam	6/19/2012	12/26/2012	9/8/2014	1/30/2015	10/5/2015	12/7/2015	5/19/2016	8/14/2017	10/23/2017	
Day of week (1 pt)	1	1	1	1	1	1	0	1	1	
Year (1 pt)	1	1	1	1	1	1	1	1	1	
State (1 pt)	1	1	1	1	1	1	1	1	1	
Money spent/have left (3 pts)	3	3	3	1	3	3	1	1	0	
Animals named (3 pts)	2	2	1	2	2	2	2	2	1	
Remember five objects (5 pts)	2	3	2	0	1	3	1	2	2	
Series of numbers, backwards (2 pts)	2	1	1	0	1	0	1	1	1	
Clock face markers (4 pts)	2	2	2	4	1	2	2	2	2	
Shapes (2 pts)	2	2	2	2	2	2	2	2	2	
Story recall (8 pts)	6	6	4	6	8	8	8	6	6	
Total Score	22	22	18	18	21	23	19	19	17	

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Cognitive Assessments Project

- OHSU Internal Medicine Clinic at Marquam Hill
  - 14,900 patients
  - 5,200 over 65 years of age (35%)
  - 352 with diagnosis of dementia
  - 40 faculty and 36 resident providers
    - 3 are Geriatricians by training
- Bi-annual Quality Incentives for faculty payment
  - Typically driven by advance payment models, institutional priorities or patient needs

https://www.ohsu.edu/xd/

- CPC+ Track 2
  - 14 Quality Metrics
  - Healthy Planet Dashboard
  - NQF 2872

NQF 2872:

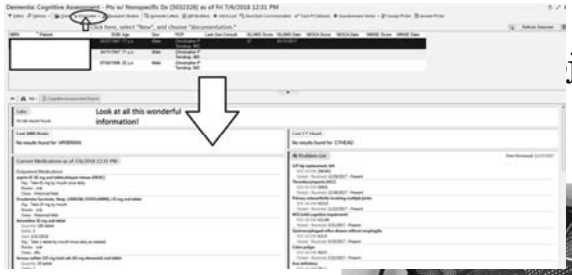
Numerator = Patients with assessment over last year

Denominator = Patients with dementia diagnosis

Why Cognitive Assessments?

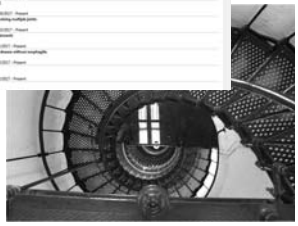
https://indyschild.com/the-mindprint-cognitive-assessment/

- Baseline Performance
  - Low at 27%
  - Goal for CPC+ 53%
- Growing importance of Dementia
- Ongoing research to expand upon
- Inter-professional Workflow
  - Important for all QI projects
  - Reducing burden on providers
- Collaboration with subspecialty colleagues
  - Discussion with Neurology colleagues
  - Utilizing subspecialty assistance

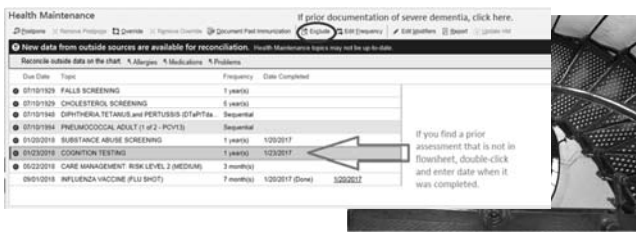


Most commonly used non-specific codes:

- Memory loss
- Memory change
- Memory concern
- Cognitive Impairment*
- Poor Memory
- Impaired Cognition

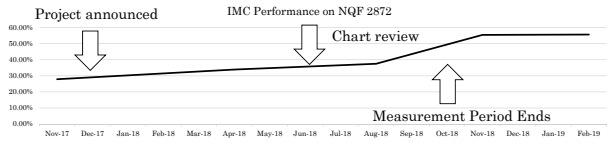


The Project



Performance

• November 2017 (baseline):	109/390	27.9%
• April 2018 (prior to chart review):	151/446	33.9%
• August 2018 (after chart review):	157/419	37.5%
• November 2018 (checkpoint):	186/335	55.5%
• February 2019 (latest update):	196/352	55.7%



In comparison

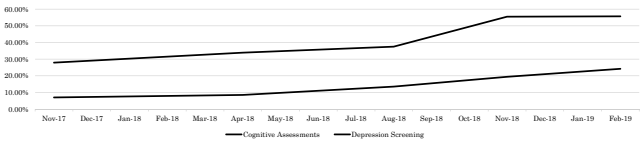
To performance on a similar metric: Depression Screening

- Nov 2017 Data not available
- Apr 2018 4753/10381 45.8%
- Aug 2018 4740/9564 49.6%
- Nov 2018 4536/9374 48.4%
- Feb 2019 4700/10243 45.9%

The Patient Health Questionnaire-2 (PHQ-2)

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not At All	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3

IMC: Cognitive Assessments versus Depression Screening

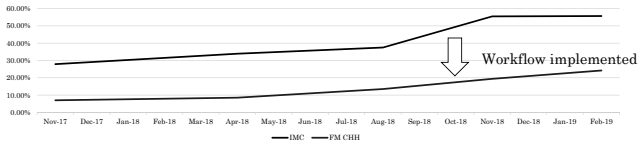


In comparison

To performance on *same* metric at a different primary care clinic

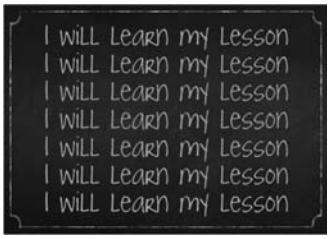
- Nov 2017 16/228 7.0%
- Apr 2018 21/247 8.5%
- Aug 2018 19/141* 13.5%
- Nov 2018 25/129** 19.4%
- Feb 2019 30/124 24.2%

Cognitive Assessments: IMC versus FM CHH



Lessons Learned

- Importance of involving all staff roles in process
- Engaging with IT support
- Utilizing local content experts
- Focusing on an impactful, patient-centered metric
- Provider education has value but chart review can move the needle
- Importance of involving all staff roles in process



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In the Clinic: 2/25/19

- Mrs. W is a 91 year old female who has been followed in our Geriatric Clinic who has a diagnosis of "dementia"; also has CKD and GERD. Comes to the clinic to meet her new provider (me) with her son and daughter-in-law.
- Medications: Donepezil 10 mg daily, Omeprazole 20 mg daily.
- Social history: Lives in independent living. Receives assistance with IADLs and some ADLs. Widowed.
- MA rooms patient, notes has not had a cognitive screening test for 1.5 years, places SLUMS form in the room.

During the Visit

- History/Medication Review
- Exam
- Cognitive Assessment

SLUMS Exam	6/19/2012	12/26/2012	9/8/2014	1/30/2015	10/5/2015	12/7/2015	9/19/2016	8/14/2017	10/23/2017
Day of week (1 pt)	1	1	1	1	1	1	0	1	1
Year (1 pt)	1	1	1	1	1	1	1	1	1
State (1 pt)	1	1	1	1	1	1	1	1	1
Money spent/have left (3 pts)	3	3	3	1	3	3	1	1	0
Animals named (3 pts)	2	2	1	2	2	2	2	2	1
Remember five objects (5 pts)	2	3	2	0	1	3	1	2	2
Series of numbers, backwards (2 pts)	2	1	1	0	1	0	1	1	1
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Shapes (2 pts)	2	2	2	2	2	2	2	2	2
Story recall (8 pts)	6	6	4	6	8	8	8	6	6
Total Score	22	22	18	18	21	23	19	19	17

Plan for Mrs. W

- Repeated labs:
  - TSH 11 → increased levothyroxine
  - Ferritin 16 → started on iron supplementation
- Home Health PT
  - Fall risk
- Higher Level of Care:
  - Looking for foster homes, memory care units

Next steps

- Information Technology Decision Support
- Ongoing monitoring of performance on the metric
- Improved Case-Finding
- Overall improvement in Dementia care

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Acknowledgements

- IMC Colleagues
  - Gray Winkler- Data Analyst
  - Melinda Luethe- Clinic Support Supervisor
  - Edwin Muniu, Emmilie McInnis and Mariela Castro Lopez- Medical Assistants
  - Elizabeth Eckstrom, MD- Geriatrician
  - Christine Mullowney, MD and Katie Bensching, MD- Quality Support
  - Paige Perry- Clinic Manager
- Office of Population Health / Healthy Planet Team
  - Steve Kassakian, MD- Associate Chief Health Information Officer, OHSU
  - Jeff Jensen- Senior Application Analyst
  - Faiza Khan, MD- Clinical Informaticist

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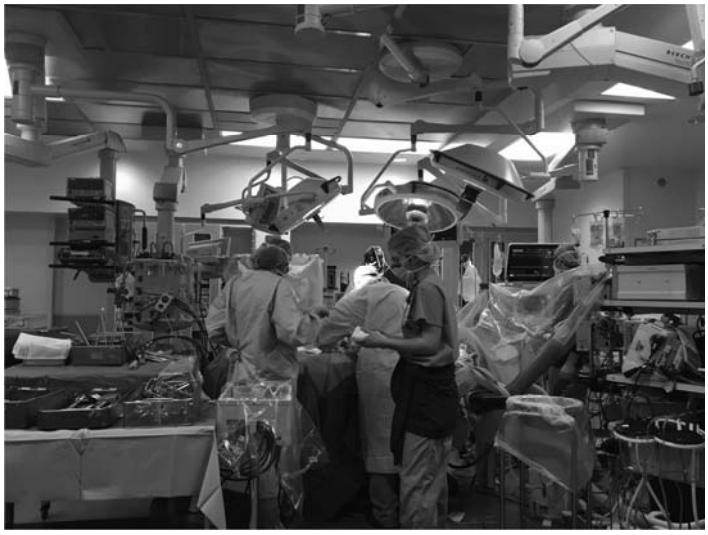
Life After the Trauma Alert

…the hidden long-term morbidity and mortality after injury.

April 11,2019 Mackenzie Cook, MD

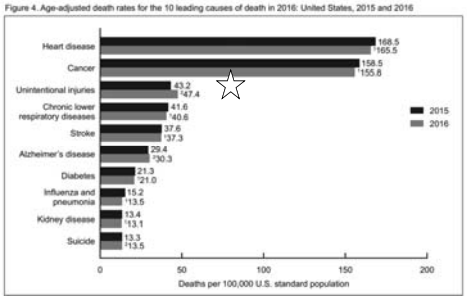


REMEMBER THIS:

Traumatic injury is a life altering event that profoundly increases a patient's risk of death and long term disability. This risk likely extends for years after injury.

3rd Leading Cause of Death

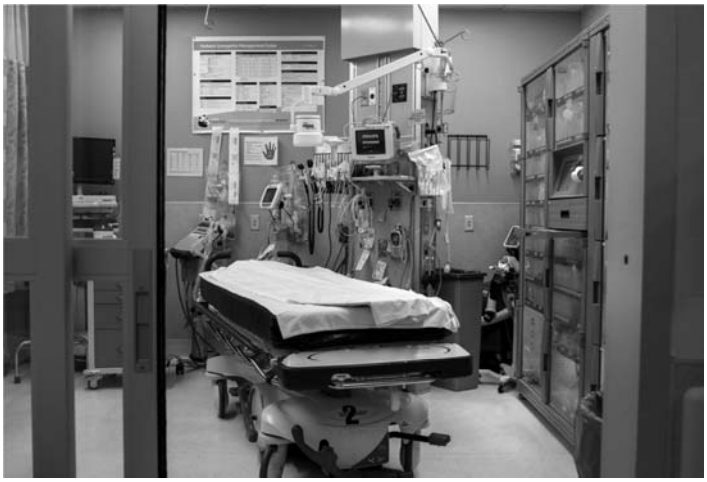
2016: 231,954 deaths due to Injury



10 Leading Causes of Death by Age Group, United States – 2016

Rank	Age Groups										
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 4,816	Unintentional Injury 1,261	Unintentional Injury 787	Unintentional Injury 847	Unintentional Injury 13,895	Unintentional Injury 23,984	Unintentional Injury 20,975	Malignant Neoplasms 41,291	Malignant Neoplasms 116,364	Heart Disease 507,118	Heart Disease 635,260
2	Short Gestation 3,927	Congenital Anomalies 433	Malignant Neoplasms 449	Suicide 436	Suicide 5,723	Suicide 7,366	Malignant Neoplasms 10,903	Heart Disease 34,027	Heart Disease 78,610	Malignant Neoplasms 422,927	Malignant Neoplasms 598,038
3	SIDS 1,500	Malignant Neoplasms 377	Congenital Anomalies 203	Malignant Neoplasms 431	Homicide 5,172	Homicide 5,376	Heart Disease 10,477	Unintentional Injury 23,377	Unintentional Injury 21,860	Chronic Low Respiratory Disease 131,002	Unintentional Injury 161,374
4	Maternal Pregnancy Comp. 1,402	Homicide 339	Homicide 139	Homicide 147	Malignant Neoplasms 1,431	Malignant Neoplasms 3,791	Suicide 7,030	Suicide 8,437	Chronic Low Respiratory Disease 17,810	Cerebro-vascular 121,630	Chronic Low Respiratory Disease 154,596
5	Unintentional Injury 1,219	Heart Disease 118	Heart Disease 77	Congenital Anomalies 146	Heart Disease 949	Heart Disease 3,445	Homicide 3,369	Liver Disease 8,364	Diabetes Mellitus 14,251	Alzheimer's Disease 114,883	Cerebro-vascular 142,142
6	Placenta Cord, Membranes 841	Influenza & Pneumonia 103	Chronic Low Respiratory Disease 68	Heart Disease 111	Congenital Anomalies 388	Liver Disease 925	Liver Disease 2,851	Diabetes Mellitus 6,267	Liver Disease 13,448	Diabetes Mellitus 56,452	Alzheimer's Disease 116,103
7	Bacterial Sepsis 583	Septicemia 70	Influenza & Pneumonia 48	Chronic Low Respiratory Disease 75	Diabetes Mellitus 211	Diabetes Mellitus 792	Diabetes Mellitus 2,049	Cerebro-vascular 5,353	Cerebro-vascular 12,310	Unintentional Injury 53,141	Diabetes Mellitus 80,058
8	Respiratory Distress 488	Perinatal Period 60	Septicemia 40	Cerebro-vascular 50	Chronic Low Respiratory Disease 206	Cerebro-vascular 575	Cerebro-vascular 1,851	Chronic Low Respiratory Disease 4,307	Suicide 7,759	Influenza & Pneumonia 42,479	Influenza & Pneumonia 51,537
9	Circulatory System Disease 460	Cerebro-vascular 55	Cerebro-vascular 38	Influenza & Pneumonia 39	Influenza & Pneumonia 189	HIV 546	HIV 971	Septicemia 2,472	Septicemia 5,941	Nephritis 41,095	Nephritis 50,046
10	Neonatal Hemorrhage 398	Chronic Low Respiratory Disease 51	Benign Neoplasms 31	Septicemia 31	Complicated Pregnancy 184	Complicated Pregnancy 472	Septicemia 897	Homicide 2,152	Nephritis 5,650	Septicemia 30,405	Suicide 44,965

Data Source: National Vital Statistics System, National Center for Health Statistics, CDC
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.



8

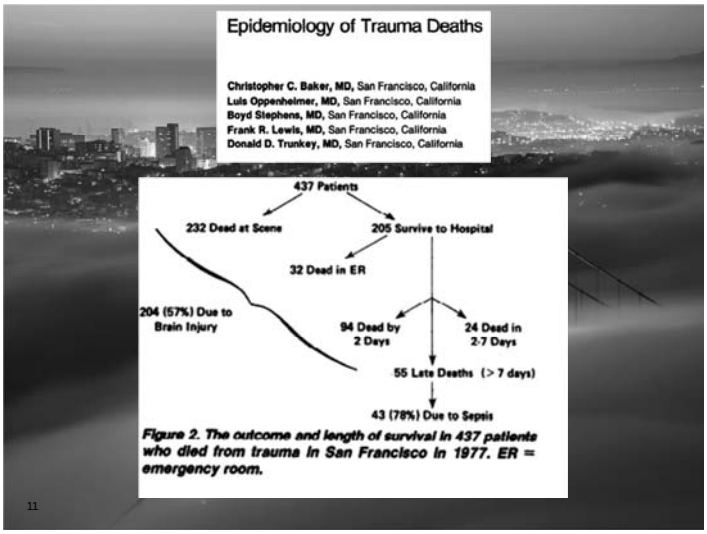
Outline and Objectives

- Death in the year after injury
- Long term psychiatric outcomes
- What are we doing?

REMEMBER THIS:

Traumatic injury is a life altering event that profoundly increases a patient's risk of death and long term disability. This risk likely extends for years after injury.

9



11

Past 40 Years of Trauma Care

- Change public policy
- Implement trauma systems
- Damage control surgery
- Improved ICU Care

Systems of Trauma Care
A Study of Two Counties
John G. West, MD; Donald D. Trunkey, MD; Robert C. Lim, MD
Arch Surg. 1979;114(4):455-460. doi:10.1001/archsurg.1979.01370280109016.

PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

PROMMTT

DAMAGE CONTROL SURGERY

THE DAMAGE CONTROL SEQUENCE AND UNDERLYING LOGIC

Michael F. Rotondo, MD, FACS, and David H. Zonies, BA, MS

PETAL NETWORK
Prevention & Early Treatment of Acute Lung Injury

Trauma Centers Work!

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

A National Evaluation of the Effect of Trauma-Center Care on Mortality

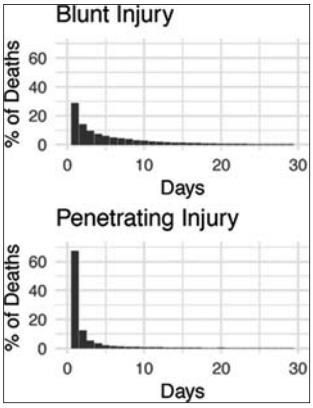
Ellen J. MacKenzie, Ph.D., Frederick P. Rivara, M.D., M.P.H., Gregory J. Jurkovich, M.D., Avery B. Nathens, M.D., Ph.D., Katherine P. Frey, M.P.H., Brian L. Egleston, M.P.P., David S. Salkever, Ph.D., and Daniel O. Scharfstein, Sc.D.

N ENGL J MED 354;4 WWW.NEJM.ORG JANUARY 26, 2006

Table 4. Adjusted Case Fatality Rates and Relative Risks of Death after Treatment in a Trauma Center as Compared with Treatment in a Non–Trauma Center.*

Variable	Weighted No. of Patients	Death in Hospital	Death within 30 Days after Injury	Death within 90 Days after Injury	Death within 365 Days after Injury
Overall population	15,009				
Trauma center (%)		7.6	7.6	8.7	10.4
Non–trauma center (%)		9.5	10.0	11.4	13.8
Relative risk (95% CI)		0.80 (0.66–0.98)	0.76 (0.58–1.00)	0.77 (0.60–0.98)	0.75 (0.60–0.95)

Modern Era



Bardes et al. J Trauma Acute Care Surg. June 2018

Trauma Solved!

...right?

Adequacy of Hospital Discharge Status as a Measure of Outcome Among Injured Patients

Richard J. Mullins, MD; N. Clay Mann, PhD, MS; Jerris R. Hedges, MD, MS; William Worrall, MA; Mark Helfand, MD; Andrew D. Zechnich, MD, MPH; Gregory J. Jurkovich, MD JAMA. 1996;276:1725-1731

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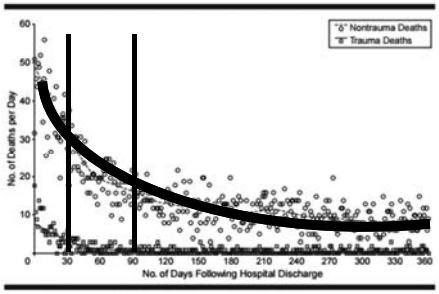


Number of deaths per day following hospital discharge for patients with trauma and nontrauma cause-of-death codes.

Things are Better Now?

Moving Beyond Traditional Measurement of Mortality after Injury: Evaluation of Risks for Late Death

Jeffrey A Claridge, MD, MS, FACS, William H Leukhardt, MD, Joseph F Golob, MD, Andrew M McCoy, BS, Mark A Malangoni, MD, FACS (J Am Coll Surg 2010;210:788–796.

Late Mortality after Trauma and its Relationship to Hospital Mortality

Variable	Mortality, %	Relative change from hospital mortality, %
Hospital	3.3	—
30-d postdischarge	3.6	9.1
90-d postdischarge	4.1	24.2
1-y postdischarge	5.2	57.6
Entire study period	8.1	145

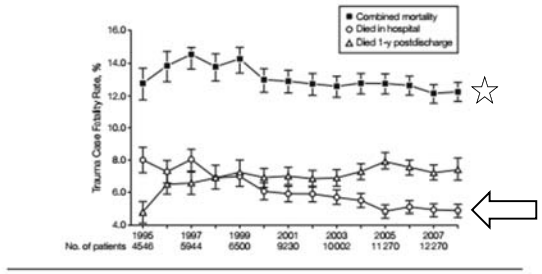
⇦ 2.8 years

Long-term Survival of Adult Trauma Patients

Giana H. Davidson, MD, MPH
Christian A. Hamlat, MD, MPH
Frederick P. Rivara, MD, MPH
Thomas D. Koepsell, MD, MPH
Gregory J. Jurkovich, MD
Saman Arbabi, MD, MPH

JAMA. 2011;305(10):1001-1007

Figure 1. Trauma Case Fatality Rate for Inpatients and 1-Year Postdischarge



Error bars indicate 95% confidence intervals.

Why do People Die after Discharge?

Good Question

Late Death After Multiple Severe Trauma: When Does It Occur and What Are the Causes?

Christian Probst, MD, Boris A. Zelle, MD, Nicola A. Sittaro, MD, Ralf Lehne, PhD, Christian Krettek, MD, and Hans C. Pape, MD

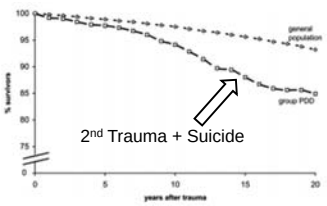


Fig. 3. *Mortality rate after the event of PDD patients and survival of an age and gender-matched German general population.*

AAST 2015 Plenary Paper

Discovering the truth about life after discharge: Long-term trauma-related mortality

Rachael A. Callcut, MD, MSPH, Glenn Wakam, Amanda S. Cooper, Lucy Z. Kornblith, MD, Benjamin M. Howard, MD, MPH, Eric M. Campion, MD, Mary F. Nelson, RN, MPA, Matthew W. Mell, MD, MS, and Mitchell J. Cohen, MD. San Francisco, California

TABLE 4. Cause of Death Distribution

	Overall (n = 245)		Out of Hospital (n = 35)	
Cause of Death	**n**	**%**	**n**	**%**
Trauma related	221	90.2	15	42.9
Cardiovascular	7	2.9	5	14.3
Infectious/sepsis	4	1.6	4	11.4
Pulmonary	1	0.4	1	2.9
Cancer	1	0.4	1	2.9
Unknown	2	0.8	2	5.7

Can we Predict who Will Die?

- Short Answers: not really
- Long answer: not really, but maybe
  - age, disposition, comorbidities

Main Points : Mortality

- We are very good at resuscitation, damage control and critical care
- Patients who used to die in the ICU now are dying at home/SNF
- Discharge is not the end of the story

REMEMBER THIS:

Traumatic injury is a life altering event that profoundly increases a patient's risk of death and long term disability. This risk likely extends for years after injury.

Outcome after Major Trauma: 12-Month and 18-Month Follow-Up Results from the Trauma Recovery Project

Holbrook, Troy L. PhD; Anderson, John P. PhD; Sieber, William J. PhD; Browner, Dierdre MPH; Hoyt, David B. MD, FACS

The Journal of Trauma: Injury, Infection, and Critical Care: May 1999 - Volume 46 - Issue 5 - p 765-773

- Quality of Well-Being scale
  - Mobility
  - Physical Activity
  - Social Activity
- **40% of patients had a poor recovery at 12 & 18 months (<90% baseline)**

26

Outcome after Major Trauma: 12-Month and 18-Month Follow-Up Results from the Trauma Recovery Project

Holbrook, Troy L. PhD; Anderson, John P. PhD; Sieber, William J. PhD; Browner, Dierdre MPH; Hoyt, David B. MD, FACS

The Journal of Trauma: Injury, Infection, and Critical Care: May 1999 - Volume 46 - Issue 5 - p 765-773

Depression and PTSD at 6 & 12 months are SIGNIFICANTLY associated with impaired quality of well being

27

The Journal of TRAUMA® Injury, Infection, and Critical Care

Predicting Quality of Life Six Months After Traumatic Injury

James M. Kiely, MD, Karen J. Brasel, MD, MPH, Kevin L. Weidner, MS , Clare E. Guse, MS, and John A. Weigelt, MD

- Poor QoL associated with:
  - Poor functional status
  - PTSD
  - Depression
  - Poor social support

- **NOT associated with Injury Severity Score**

28

Main Points : Quality of Life

- A significant fraction of our patients do not recover to their pre-injury baseline
- Depression and PTSD are SIGNIFICANT predictors of poor QoL

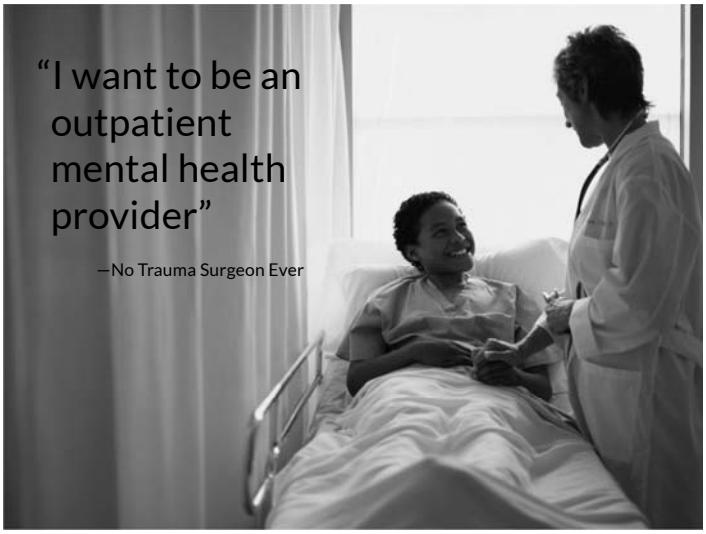
REMEMBER THIS:

Traumatic injury is a life altering event that profoundly increases a patient's risk of death and long term disability. This risk likely extends for years after injury.

29

What Can We Alter?

- Complication rate
- Pre-injury functional status
- Social / medical support
- PTSD
- Depression



PTSD after Civilian Trauma

PTSD in civilian populations after hospitalization following traumatic injury: A comprehensive review

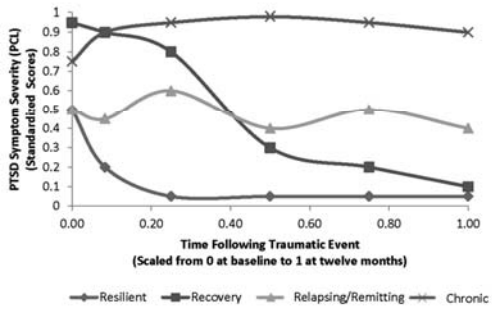
Carolina Stefany Paredes Molina, MD, Stepheny Berry, MD, Alexandra Nielsen, MD, Robert Winfield, MD MPH
The University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS, 66160, USA

- 65 studies from 1992 – 2017
- 20-40% of trauma survivors with PTSD within a year
- No standard screening tool
- No standard intervention

Civilian PTSD Trajectory

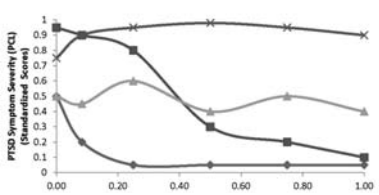
Exploring the Longitudinal Trajectories of Posttraumatic Stress Disorder in Injured Trauma Survivors

Janyce E. Oseitbach, Charles Lewis, Barry Rosenfeld, Joan Russo, Leah M. Ingraham, Roselyn Peterson, Jin Wang, and Douglas F. Zatzick



Civilian PTSD Trajectory

- Multiple overlapping PTSD trajectories early
- Very few patients recover if showing early signs
- Support for development of early intervention



A Really, Really Big Deal

- "A plan to evaluate, support, and treat PTSD should be considered"
- "Routine screening for depression…is prudent"

We Need Your Help

We Can do this Better!

- How do we track outcomes?
- How do we predict PTSD / depression?
- How do we intervene effectively?

We Can do this Better!

- How do we track outcomes?

- How do we predict PTSD / depression?
- How do we intervene effectively?

We Can do this Better…with Friends!

AAST 2016 Plenary Paper

Utility of the injured trauma survivor screen to predict PTSD and depression during hospital admission

Joshua C. Hunt, PhD, Marty Sapp, EdD, Cindy Walker, PhD, Ann Marie Warren, PhD, Karen Brasel, MD, MPH, *and* Terri A. deRoon-Cassini, PhD, *Milwaukee, Wisconsin*

Injured Trauma Survivor Screen (ITSS)

1 = Yes 0 = No

Before this injury	PTSD	DEP
1. Have you ever taken medication for, or been given a mental health diagnosis?		1 0
2. Has there ever been a time in your life you have been bothered by feeling down or hopeless or lost all interest in things you usually enjoyed for more than 2 weeks?		1 0
When you were injured or right afterward		
3. Did you think you were going to die?	1 0	1 0
4. Do you think this was done to you intentionally?	1 0	
Since your injury		
5. Have you felt emotionally detached from your loved ones?		1 0
6. Do you find yourself crying and are unsure why?		1 0
7. Have you felt more restless, tense or jumpy than usual?	1 0	
8. Have you found yourself unable to stop worrying?	1 0	
9. Do you find yourself thinking that the world is unsafe and that people are not to be trusted?	1 0	
≥ 2 is positive for PTSD risk ≥ 2 is positive for Depression risk SUM =		

Predicting PTSD/Depression

AAST 2017 Podium Paper

Six-month follow-up of the injured trauma survivor screen: Clinical implications and future directions

Joshua C. Hunt, PhD, Samantha A. Chesney, MS, Karen Brasel, MD, *and* Terri A. deRoon-Cassini, PhD, *Milwaukee, Wisconsin*

- ITSS PTSD: Sensitivity: 85%, NPV: 92%
- ITSS Depression: Sensitivity: 73%, NPV: 92%

OHSU recruiting for MITSS

We Can do this Better!

- How do we track outcomes?
- How do we predict PTSD / depression?
  - MITSS
- How do we intervene effectively?

Multi-Tier Approach to Psychological Intervention of Traumatic Injury (MAPIT)

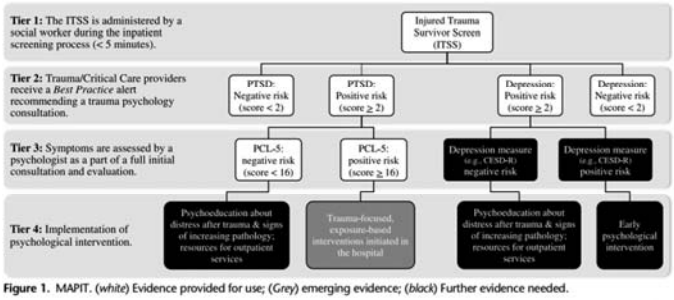


Figure 1. MAPIT. (*white*) Evidence provided for use; (*Grey*) emerging evidence; (*black*) Further evidence needed.

We Need Your Help

Main Points : PTSD / QoL

- Impaired quality of life after injury is common
- ALMOST HALF of our patient have persistent psychiatric impairments
- We have functionally NO screening / interventions in place

REMEMBER THIS:
Traumatic injury is a life altering event that profoundly increases a patient's risk of death and long term disability. This risk likely extends for years after injury.

Trauma Care is Generational

Patients SURVIVING long enough to suffer from PTSD / Depression / Depressed QoL

REMEMBER THIS:

Traumatic injury is a life altering event that profoundly increases a patient's risk of death and long term disability. This risk likely extends for years after injury.

Harmful polypharmacy

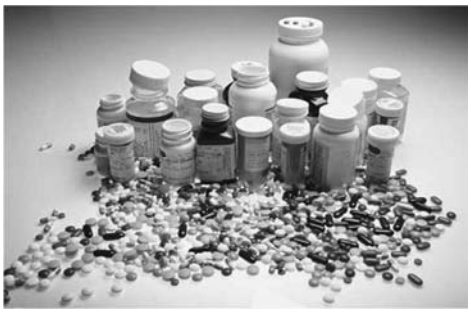
Arthur D. Hayward, MD, MBA

Harmful polyp**har m**acy

Arthur D. Hayward, MD, MBA

I have nothing to disclose.

Case Study: Does Verda need pravastatin?



Outline

(And, But, Therefore)

- Our era of medicine is dominated by new and powerful drugs
- But drug overuse risks harm
- We must use drugs judiciously and cautiously.

The Enlightened Era of Drugs

- Previously untreatable diseases are now treatable, **and**
- Formerly hospitalized are now treatable as outpatients, **and**
- Longevity has increased, **and**
- Some costs have decreased. (?)
- **But…**

But…Do we overemphasize drugs?

- Commercialization and its imperatives*
- Medicalization of normal states and conditions
- Misleading claims and marginal benefits
- Increased risk of adverse effects[1] *
- Rising costs*
- Neglect of non-drug treatment[2] *
- Public Disillusionment

[1]Qato DM. JAMA Intern Med. Changes in Prescription… 2016 Apr;176(4):473-82.
[2]Ioannidis. Comparative Effectiveness of Exercise…BMJ 2013;347:f5577

Commercialization

Increase revenue (shareholder value)

- Invent new drugs
- Sell more current drugs
  - Increase demand
    - Expand the market
      - Add indications (antipsychotics)
      - Extend treatment (statins, opioids)
      - Ensure Insurance coverage (Medicare, private insurers)
    - Penetrate more of the existing market (statins)
      - Advertising and promotion[1]
        - Direct to consumers ($2.1 to 9.6B)
        - To opinion leaders and prescribers ($15.6 to 20.3B)
      - Help generate and promote guidelines
      - Lower prices??
  - Outcompete
    - Extend patents
- Raise prices

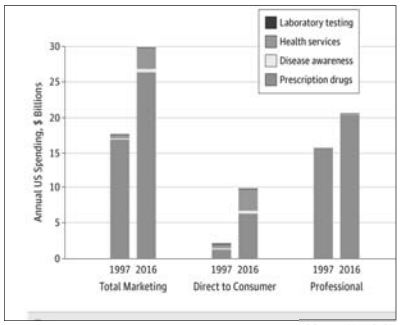
[1]Schwartz LM, Woloshin S. Medical Marketing… 1997 to 2016. JAMA. 2019;321(1):80-96

Promotion/ Advocacy/ Hype

- The term "miracle drug" came into use around 1944 to refer to a substance "that elicits a dramatic response in a patient's condition".
  (Merriam Webster Dictionary)
- In 2015 in one 4-day span 94 articles from 64 distinct news outlets used "miracle" or synonyms like "break-through" or "game changer" referring to 36 specific new oncology drugs, half not yet approved by the FDA and several not trialed in humans.

Abola MV, Prasad V. Research Letter. JAMA Oncol. 2016:2(1);139-141

Changes in Medical Marketing Costs 1997 -2016



Schwartz LM, Woloshin S. Medical Marketing… 1997 to 2016. JAMA. 2019;321(1):80-96

Rising costs of drugs

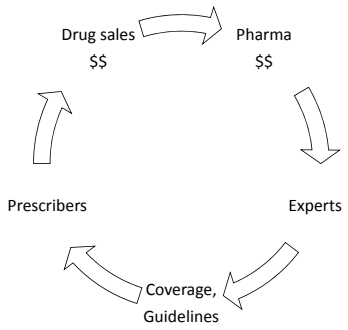
- In 2016 the US spent $3,337 billion on national health expenditures and $329 billion on prescription drugs[1].
- CMS projects spending for retail prescription drugs will be the fastest growth health category over the next decade[2].

[1]Hartman, M et al. National Health Care Spending…. Health Affairs 37(1):150-160. Jan 2018
[2]Cuckler G et al. National Health Expenditure…Health Affairs 37(3); March 2018.

New Drug Approvals

Podcast: Vinay Prasad

Drug Dissemination



Adverse Drug Effects (ADEs)

- Pre-approval Phase Three trials may not detect infrequent ADEs.
- Interactions may be unpredictable, multiple.
- ADEs can be undetected/ under-reported in clinical practice.
- Prescribing patterns often do not change despite known risks.
  - Anticholinergics and antipsychotics in patients with dementia
- Mistaking ADEs as new problems to be treated risks creating the *prescribing cascade*.

The Prescribing Cascade

Do we neglect non-drug treatment?

Exercise

Diet

Sleep

Ioanidis J. BMJ 2013;347:f5577 doi: 10.1136/bmj.f5577 (Published 1 October 2013)

Polypharmacy in Preventive Cardiology[1]

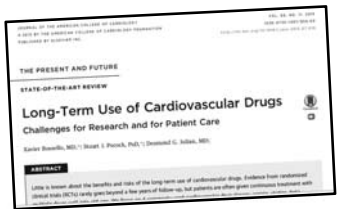
Problem: Millions on CVD drugs* though proof of benefit lacking.

- Short-term study results are extrapolated over decades.
- Results from young-old subjects are extrapolated to old-old.
- We have scant evidence on outcomes of drug withdrawals.
- Modern clinical practice differs from that when trials were conducted.
- Projections of benefits assume hazards are constant over time.
- Old-old adults may prefer different outcomes.

*Aspirin, beta-blockers, statins, ACE inhibitors

➢ **How long should these drugs be continued?**

[1]J Am Coll Cardiol 2015;66:1273


THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Long-Term Use of Cardiovascular Drugs

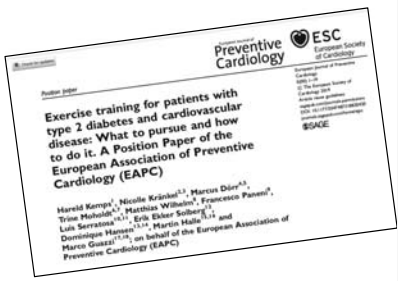
Challenges for Research and for Patient Care

ABSTRACT

European Association of Preventive Cardiology

Exercise training recommended for Type II diabetics with CV disease

- Target dysglycemia, dyslipidemia, arterial hypertension, obesity, reduced cardiovascular fitness
- Improve insulin sensitivity, lipid profile, vascular reactivity, CV fitness, (inflammation?)
- Mounting evidence (200+ references)
- => Prescribe exercise training
  - How-to recommendations based on individual patient profiles.


Preventive Cardiology

ESC European Society of Cardiology

Exercise training for patients with type 2 diabetes and cardiovascular disease: What to pursue and how to do it. A Position Paper of the European Association of Preventive Cardiology (EAPC)

SAGE

https://doi.org/10.1177/2047487318820420 (Euro J of Prev Cardiology Jan. 14, 2019)

Therefore…??

A. Scrutinize literature carefully and skeptically.
B. Consider drug alternatives[1].
C. Use safer drugs[2].
D. Investigate possible adverse effects in your patients.
E. Consider time-to-benefit vs longevity when prescribing.
F. Deprescribe?

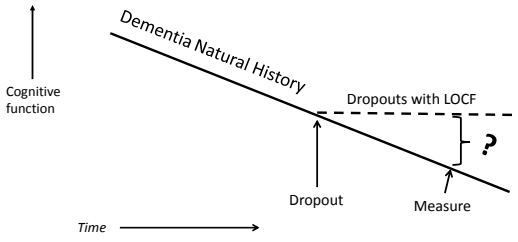
[1] Trauer JM, Cunnington D. CBT for Chronic Insomnia… Ann Intern Med. 2016 Jan 19;164(2):134-5.
[2] Hanlon JT, Semla TP, Schmader KE. J Am Geriatr Soc. Alternative Medications… 2015 Dec;63(12):e8-e18.

Scrutinize Clinical Trials Carefully

1. Doublecheck funding sources and disclosures.
2. Consider methodology
   a. Note Exclusions.
      I. By age
      II. By co-morbidities
   b. Is statistical significance clinically meaningful?
3. Ask whether findings have been reproduced in subsequent studies.
4. Consider misconduct including falsification of data[1].

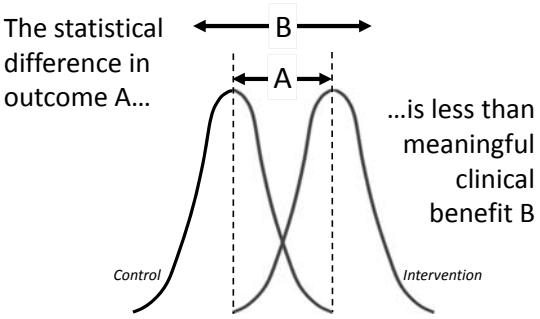
[1] Seife C. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature. JAMA Intern Med. 2015;175(4):567-577. doi:10.1001/jamainternmed.2014.7774

Last Observation Carried Forward Methodology



Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, van den Bussche H. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomized clinical trials. BMJ. 2005 Aug 6;331(7512):321–7.

"Statistical Error Type 3"



See Lin JS, O'Connor E, et al. "Screening for Cognitive Impairment…" *Ann Intern Med.* 2013;159(9):601-612.

Failures of Replication


ORIGINAL CONTRIBUTION

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

The Decline Effect

Ioannidis Reviewed 49 high impact treatment or prevention studies 1990 - 2003
- 5 found no benefit

Of 44 studies claiming benefit…
- 11 not repeated
- 7 contradicted
- 7 found less efficacy

=> 14 of 33 (42%) of positive studies not confirmed

Ioannidis. JAMA. 2005 Jul 13;294(2):218-28.

Therefore…Deprescribe?

- Yes? (benefits)
- Why not?? (obstacles)

Benefits

Reduce
- Pill Burden
- confusion
- risks of potential adverse and of under-recognized drug effects
- paperwork and tasks of drug reconciliation
- costs of care
- nursing burden

Increase
- Use of non-drug treatment
- therapeutic alliance

Obstacles to Deprescribing

- Profiling and guidelines
- Reversing decisions by other prescribers
- Self-contradicting previous decisions
- Time constraints
- Patient choice…some of the time
- Treatment imperative

Why Don't (VA) PCPs Deprescribe?

<u>Survey results:</u>

Lack of awareness

(39% not aware tight glucose control harms older adults)

Fear of bad report card (42%)

Fear of legal liability (25%)

Not enough time to discuss (30%)

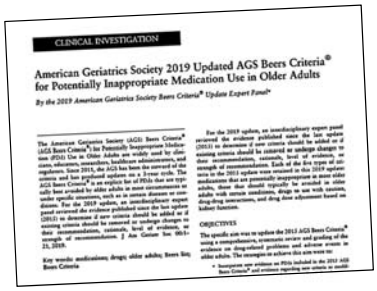
JAMA Intern Med. 2015;175(12):1994-1996. doi:10.1001/jamainternmed.2015.5950

Why and how we/ you deprescribe?

How?

- Solicit patient ideas and priorities
- Go Step-by-Step
- Offer alternatives
- Get help*
  - Pharmacy specialists
  - Consult authoritative sources
- Follow-up
- Add "polypharmacy" to the problem list

2019 updated Beers Criteria



CLINICAL INVESTIGATION

American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults

By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel*

<u>For adults 65 and older</u>

1. Evidence scheme
2. Potentially inappropriate in most
3. Drug Disease issues
4. Use with caution
5. Drug-Drug issues
6. Renal toxicity concern
7. Anticholinergics
8. Meds removed
9. Meds added

http//:deprescribing.org

J Am Geriatr Soc. 2019 Jan 29. doi: 10.1111/jgs.15767. [Epub ahead of print]

Non-Drug Treatment For Behavioral and Psychiatric Symptoms of Dementia (BPSD)[1]

Sensory
- Massage
- Multi-sensory
- Aromatherapy

Stimulation
- Bright light

Psychosocial practices
- Validation therapy
- Reminiscence therapy
- Music therapy
- Pet
- Meaningful activities

Structured care protocols
- Bathing
- Mouth care

[1]Scales, et al. Gerontologist, 2018, Vol. 58, No. S1, S88–S102

Non-Drug Treatment

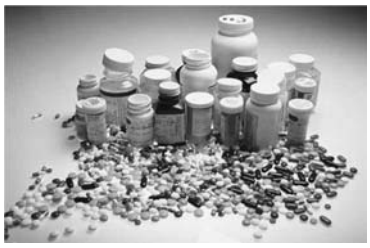
- For BPSD[1]
  - Sensory
    - Massage
    - Multi-sensory
    - Aromatherapy
  - Stimulation
    - Bright light
  - Psychosocial practices
    - validation therapy
    - reminiscence therapy
    - music therapy
    - pet
    - meaningful activities
  - Structured care protocols
    - bathing
    - mouth care

Individualized Nurse Interventions

- Model desired behavior
- Avoid arguing
- Engage in social interaction
- Use non verbal communication
- Identify and avoid triggers
- Redirect
- Recruit for "meaningful" activity
- Provide live or inanimate pets

[1]Scales, et al. Gerontologist, 2018, Vol. 58, No. S1, S88–S102

Case Study: Does Verda need pravastatin?



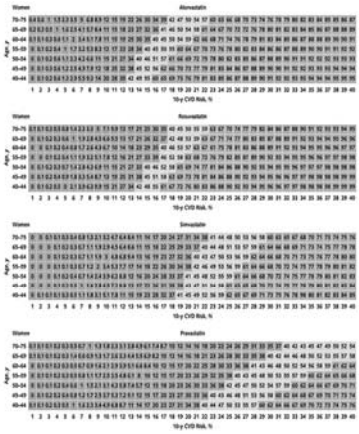
Michael A. Steinman; Joseph T. Hanlon Managing Medications in Clinically Complex Elders "There's Got to Be a Happy Medium"
http://jama.ama-assn.org/cgi/content/full/304/14/1592
JAMA. 2010;304(14):1592-1601 (doi:10.1001/jama.2010.1482)

Finding the balance between benefits and harms from statins for primary prevention

A "balance modeling" study
Individualizes statin therapy recommendations
by drug, patient age, sex, and calculated risk of ADEs and CV outcomes, including weighted preferences
using these data sources:
CV risk calculations, meta-analysis of statin trials, and observational studies, time horizons, and weightings from surveys of patient preference
to generate granulated heat maps.

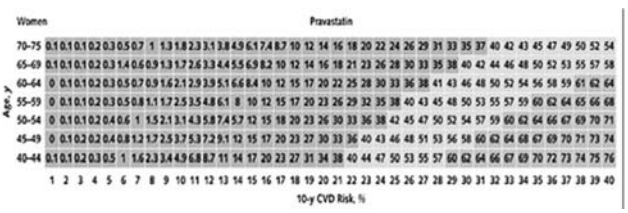
Yebyo HG et al. Finding the Balance Between Benefits and Harms When Using Statins for Primary Prevention of Cardiovascular Disease. Ann Intern Med: 2019;170:1-10.

Probabilities at which statin therapy for primary prevention of CVD is likely to provide net benefits among 1120 subgroups of women based on age 40 - 75, CVD risk (1% to 40%), statin type, and potential for drug harm.



Henock G. Yebyo, MSc; He˙le˙ne E. Aschmann, MSc; and Milo A. Puhan, MD, PhD. Finding the Balance Between Benefits and Harms When Using Statins for Primary Prevention of Cardiovascular Disease A Modeling Study. Ann Intern Med. 2019;170(1):1-10.

If Verda is 75 years old there is no 10-year CV risk level at which benefits outweigh risks



Conclusions

Pharmaceutical products have greatly assisted prescribers in relieving the burdens of illness..,

BUT

claims of benefits can overstate their efficacy and tend to understate potential harms...

THEREFORE,

prescribers are obliged to carefully weigh both scientific claims and patient preferences and to recognize that the best treatment is sometimes not a drug.

Questions?

Medications for Opioid Use Disorder: Who Should Get What When

Jessica Gregg, MD, PhD
OHSU Addiction Medicine Section
OHSU Internal Medicine Review, April 11, 2019

Disclosure Information

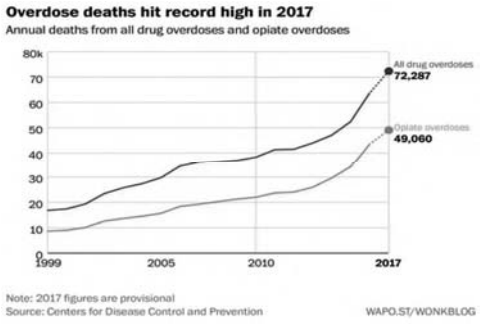
I have nothing to disclose

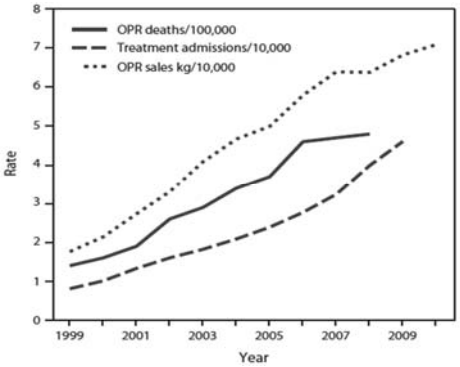
Objectives:

1. Challenge the idea that the opioid crisis is simply a problem of overprescribing

2. Compare medications to treat opioid use disorder in terms of:

    a) Efficacy (on a stable dose)
    b) Induction, retention, and other clinical variables
    c) Operational/Systems level constraints





MMWR Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999--2008
Weekly November 4, 2011 / 60(43);1487-1492

Higher prescribed opioid doses correlates with increased risk of overdose

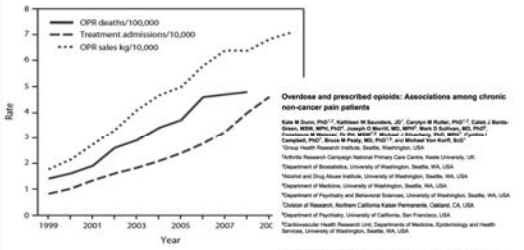
Higher doses and longer use correlates with increased risk of developing an opioid use disorder

Edlund et al Clin J Pain 2014
Dunn KM, et al. *Ann Intern Med*. 2010
Braden JB. *Arch Intern Med*. 2010
Bohnert AS, et al. *JAMA*. 2011
Paulozzi LJ. *Pain Med*. 2012

Opioids have only fair evidence for moderate relief of chronic pain

Little evidence that opioids are better than interventions such as NSAIDs, CBT, or exercise therapy for conditions like chronic low back pain

Furlan AD, et al CMAJ. 2006;
Ballantyne JC, Shin NS. Clin J Pain. 2008
Noble M et al Cochrane Database Syst Rev. 2010
Chou, Annals of Internal Medicine 2015

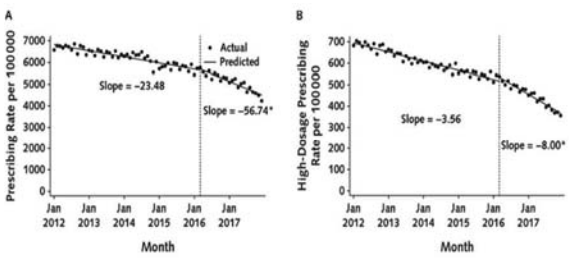


Overdose and prescribed opioids: Associations among chronic non-cancer pain patients

CDC Guideline for Prescribing Opioids for Chronic Pain

March 2016

Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016.

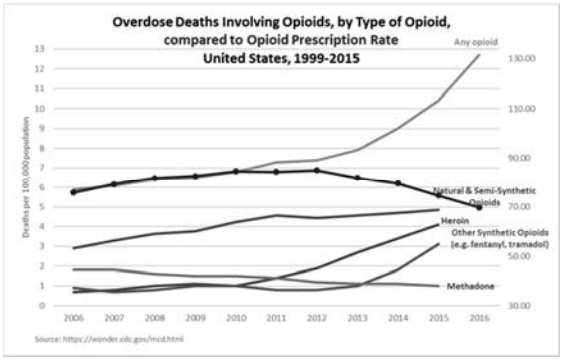


Bohnert, ASB et al Annals of Intern Med 2018

Increase rx → increase OD

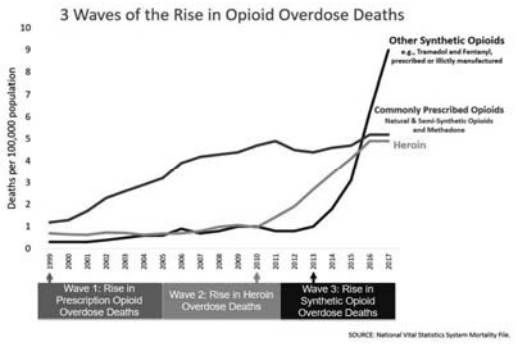
Decrease rx --> ???

Increased Overdose



An expanded pool of susceptible individuals

A supply side strategy that was not balanced with efforts to engage and retain people with opioid use disorder or poorly managed pain



Cicero TJ[1], Ellis MS[2], Kasper ZA[2]. Addict Behav 2017

From 2016 to 2017: Nationally

45% increase in fentanyl overdose

Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G MMWR 2019

From 2016 to 2017: Oregon

90.9% increase in fentanyl overdoses

Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G MMWR 2019

Summary

Judicious opioid prescribing is important

A supply side strategy must be balanced with efforts to engage and retain people with opioid use disorder or poorly managed pain

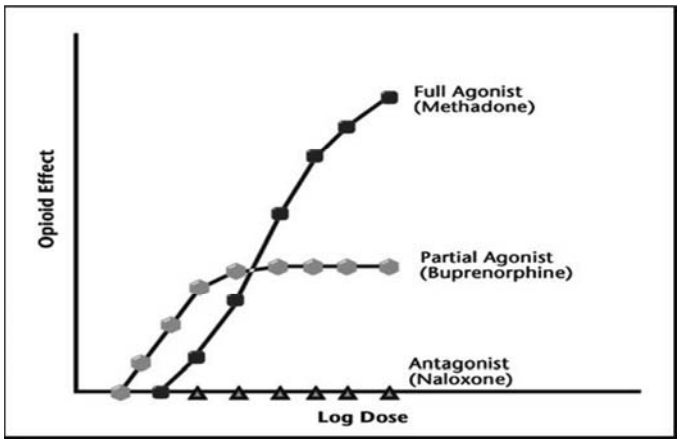
We need to look beyond prescribing limits to effectively intervene in this crisis

Objectives:

1. Challenge the idea that the opioid crisis is simply a problem of overprescribing

2. Compare medications to treat opioid use disorder in terms of:

    a) Efficacy (on a stable dose)
    b) Induction, retention, and other clinical variables
    c) Operational/Systems level constraints



Methadone

Full agonist at the mu opioid receptor

Half life greater than 24 hours

Only available through opioid treatment program (OTP)

Highly regulated

Methadone: efficacy

Cochrane review 2009: methadone v treatment without medication

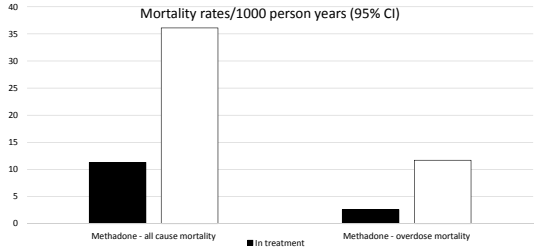
Patients on methadone significantly less likely to have positive urine drug screen

Fewer new infections with Hep C/HIV

Decreased criminality

Mattick RP, et al. *Cochrane Database of Systematic Reviews* 2009

Mortality Risk during and after methadone treatment



Mortality Risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Sordo, et al. BMJ 2017.

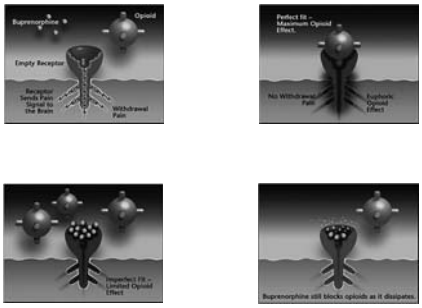
Buprenorphine

Partial agonist at the mu opioid receptor

Half life greater than 24 hours

Can be prescribed outside of an OTP by a provider with a DATA waiver

How Does Buprenorphine Work?



Adapted from slide by Todd Korthuis, MD

Buprenorphine: efficacy

Cochrane review 2014: buprenorphine v methadone

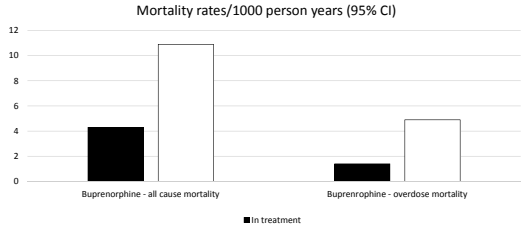
low dose, medium dose, high dose, or flexible dosing

Buprenorphine was equivalent to methadone for suppression of illicit drug use except at low doses

No significant difference in mortality

Mattick RP, et al. *Cochrane Database of Systematic Reviews* 2014.

Mortality Risk during and after buprenorphine treatment



Mortality Risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Sordo, et al. BMJ 2017.

Fewer than 5% of physicians prescribe

Jaffajee RL et al Am J of Preventive Med 2018
President's Commission on Combatting Drug Addiction and the Opioid Crisis, Nov 1 2017

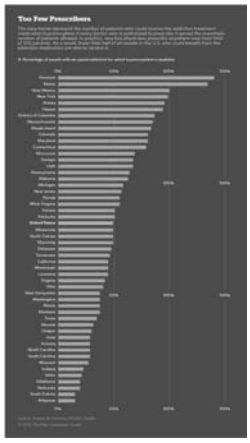
47% of counties nationwide do not have a DATA waived physician

72% of rural counties, do not have a DATA waived physician

President's Commission on Combatting Drug Addiction and the Opioid Crisis, Nov 1 2017

US

Oregon



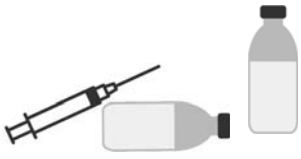
Mid-2016:
467 DO's and MD's DATA waived
23-26% had written at least one prescription

Mid-2017:
544 providers DATA waived (including 20 NPs/PAs)
35% had written at least one prescription

Mid 2018:
820 providers DATA waived (including +/- 130 NPs/PAs)
57% had written at least one prescription

Personal Communication, John McIlveen, Manager, **OHA** State Opioid Treatment Authority

Naltrexone for Extended Release Injectable Suspension

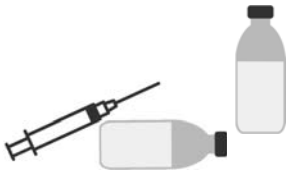


Naltrexone ER

Antagonist at the mu opioid receptor

Intramuscular injection lasts 28 days

Also effective for the treatment of alcohol use disorder



Tanum JAMA Psychiatry 2017
Lee Lancet 2017

Naltrexone ER: efficacy

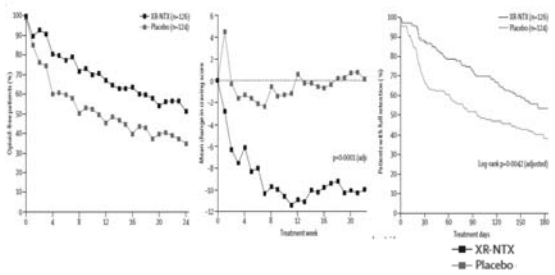
Efficacious compared to placebo:

Comer: 60 U.S. heroin users, 8 weeks (retention in tx and opioid negative urines)

Krupitsky: 250 Russian heroin users, 24 wks (retention in tx without relapse)

Comer Arch Gen Psych 2006
Krupitsky Lancet 2011

Naltrexone ER: Efficacy



Krupitsky et al., 2011

Naltrexone ER: efficacy

Efficacious compared to buprenorphine:

Tanum: Non-inferior to buprenorphine for decreasing opioid use at 12 wks

Lee: Non-inferior to buprenorphine for decreasing opioid use at 24 weeks

Tanum JAMA Psychiatry 2017
Lee Lancet 2017

Outcome	XR-NXT (n=283)	BUP-NX (n-287)	Treatment Effect
Inducted to study medication (ITT)	204 (72%)	270 (94%)	OR 0.16, 0.09-0.28; P<0.0001
Relapse-free survival (weeks)	8.4 (3-23.4)	14.4 (5.1-23.4)	HR 1.36, 1.10-1.68; p=0.0040
	20.4 (5.4-23.4)	15.2 (5.7-23.4)	HR 0.92, 0.71-1.18, p=0.49
Opioid relapse, weeks 3-24	185 (65%)	163 (57%)	OR 1.44, 1.02-2.01; p=0.036
	106/204 (52%)	150/270 (56%)	OR 0.87, 0.60-1.25; p=0.44

Lee JD, et al. *Lancet* 2017

Efficacy: conclusions

All three medications are efficacious **once a patient is on the medication**

Buprenorphine is equivalent to methadone in terms of decreased illicit drug use

Extended release naltrexone is equivalent to buprenorphine in terms of decreased illicit drug use

Both buprenorphine and methadone decrease mortality by more than ½ for patients with OUD

Objectives:

1. Challenge the idea that the opioid crisis is simply a problem of overprescribing

2. Compare medications to treat opioid use disorder in terms of:

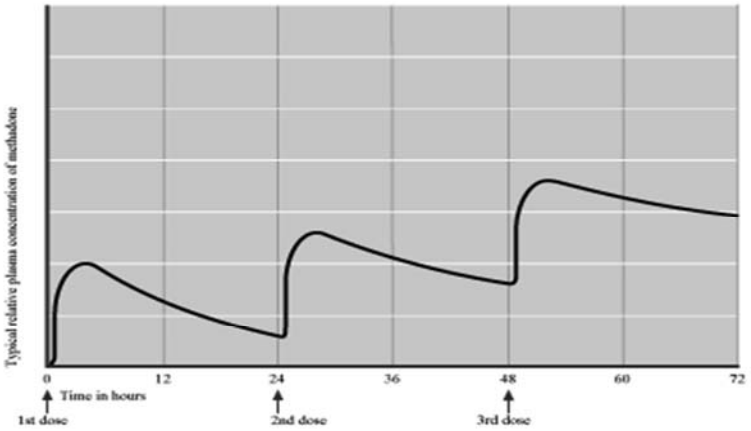
    a) Efficacy (on a stable dose)
    b) Induction, retention, and other clinical variables
    c) Operational/Systems level constraints

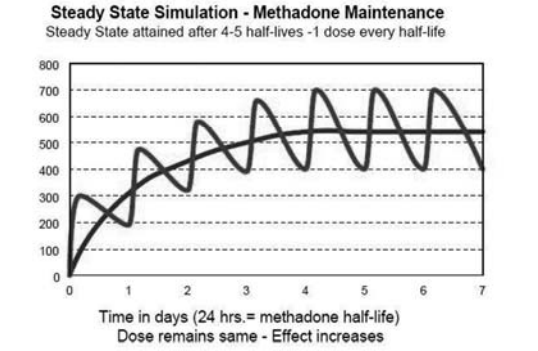
Methadone induction

No need for withdrawal

BUT the risk of death while on methadone is highest during the initial four weeks of treatment, the induction phase

Mortality Risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Sordo, et al. BMJ 2017.





In the graph above the wavy line represents the blood levels of methadone as well as the "effect" it has on the individual patient.

Buprenorphine induction

Requires a brief period of withdrawal (usually 12 – 18 hours off of opioids)

No increased mortality during induction

Clinical Opiate Withdrawal Scale (COWS)

Naltrexone ER induction

Requires abstinence from opioids 4 – 7 days

About 25% of patients will not complete induction

Outcome	XR-NXT (n=283)	BUP-NX (n-287)	Treatment Effect
Inducted to study medication (ITT)	204 (72%)	270 (94%)	OR 0.16, 0.09-0.28; P<0.0001
Relapse-free survival (weeks)	8.4 (3-23.4)	14.4 (5.1-23.4)	HR 1.36, 1.10-1.68; p=0.0040
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	106/204 (52%)	150/270 (56%)	OR 0.87, 0.60-1.25; p=0.44

Lee JD, et al. *Lancet* 2017

Summary

Methadone induction is associated with highest risk of mortality on the medication

Buprenorphine induction requires a brief period of withdrawal and is not associated with increased mortality

Almost 30% of patients are unable to tolerate induction to Naltrexone ER

What about retention?

Highest mortality **out of treatment** is in first four weeks off methadone and buprenorphine

For methadone, the highest risk of mortality **in treatment** is in the first four weeks on methadone

??? risk of overdose after cessation of naltrexone ER

Persistent engagement is critical

Retention: methadone v. buprenorphine

- Methadone is better than buprenorphine at retaining patients in care at lower doses and with flexible dosing
- Methadone is equivalent to buprenorphine at retaining patients in care at medium and high doses

Mattick RP, et al. *Cochrane Database of Systematic Reviews* 2014.

Retention: naltrexone ER

Discontinuation rates of extended release naltrexone are at least two times higher than discontinuation rates of SL buprenorphine.

More than half of those discontinuations occur after the first injection

Morgan JR, et al. JSAT 2016

Summary

Methadone retains patients slightly better than buprenorphine

Due to increased mortality with cessation of medication, persistent engagement is critical when people need the medication, and extreme care should be taken when tapering

Other clinical/patient level considerations

Prolonged QT, family hx of arrhythmia or sudden death – methadone risk

Known need for opioids in the future (surgery, sickle cell) – Naltrexone contraindication

Safe place to store medication - methadone,buprenorphine consideration

Other use disorders

Objectives:

1. Challenge the idea that the opioid crisis is simply a problem of overprescribing

2. Compare medications to treat opioid use disorder in terms of:

    a) Efficacy (on a stable dose)
    b) Induction, retention, and other clinical variables
    c) Operational/Systems level constraints

Operational/Systems variables: methadone

When used to treat an OUD, can only be dispensed only from an opioid treatment program

Patients are eligible only if they have an OUD and have had it for a least a year prior to admission (exceptions: incarceration, pregnant, previous methadone treatment)

Requirements: daily dispense for a minimum of 90 days, perhaps more

+/-insurance

Operational/Systems variables: buprenorphine

Provider with a DATA waiver

Clinic level support (help with UDS, tracking numbers of patients, PDMP, refills)

+/- space for inductions

Insurance coverage has (mostly) become less of a barrier

Operational/Systems variables: XR naltrexone

Insurance coverage

Clinician comfort

	Methadone	Buprenorphine	Naltrexone ER
Available?	+	+	+
Does your patient need daily dispense?	+	+/-	n/a
Is daily dispense problematic (illness, geography)?	X	+	+
Does your patient have a place to store medication?	+/-	+	n/a
Will your patient require opioids in the future?	+	+	X
Is a period of abstinence unlikely/difficult?	+	+/-	X
Does your patient want this medication?	+	+	+
Other clinical variables	+	+	+

Conclusion

To effectively address the opioid crisis, we need to treat opioid use disorder

Each of you can make a difference

Get waivered

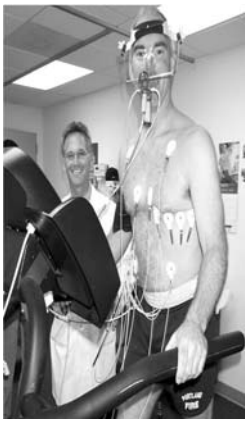
Thank you

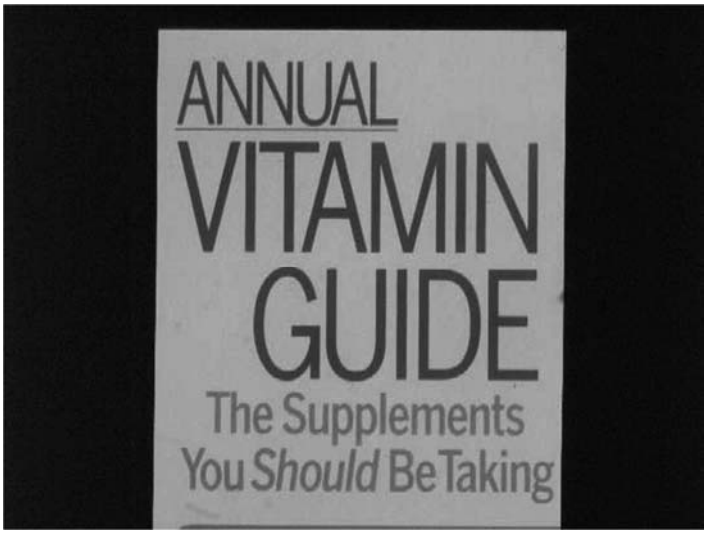
Dietary Supplements: Help Hype or Harm

Kerry Kuehl, M.D., Dr.P.H., M.S.
Professor of Medicine
Chief Health Promotion and Sports Medicine
Director Human Performance Laboratory
Oregon Health & Science University

Human Performance Laboratory

- Health Risk Assessment
- Blood and biomarkers
- Body composition analysis
- Cardiopulmonary Exercise Testing
- Basal Metabolic Rate measurement
- Dietary analysis and prescription
- Weight loss counseling
- Elite athlete testing and training
- Sports nutrition and supplements
- Research: diet and exercise as Med Rx





Dietary Supplement Types

- Vitamins
- Minerals
- Herbs or Botanicals
- Sports Supplements
- Thermogenic or Weight Loss Products
- Essential Fatty Acids
- Probiotics
- Fiber

SPORTS SUPPLEMENTS

- Energy Drinks (Gatorade, Red Bull, etc.)
- Bars and Gels (Powerbar, Supergel)
- Amino Acids (Arginine, BCAA, Creatine)
- Protein Powders (Whey, Casein)
- Minerals (Calcium, Iron, etc)
- Stimulants (Ephedrine, Caffeine, etc)
- Anabolic Precursors (DHEA, Andro, etc)
- Vitamins (Vit B, C, folate, etc)

Top 10 Supplements of 2018

- Multivitamin
- Calcium
- Vitamin D
- Omega-3 (EPA and DHA) Fatty Acids
- Probiotics
- Whey Protein
- Glucosamine/Chondroitin
- Vitamin C
- Sports drinks
- Psyllium(soluble fiber)

History of Supplement Use

Initial Use: Treatment and prevention of micronutrient deficiencies with vitamins and minerals.

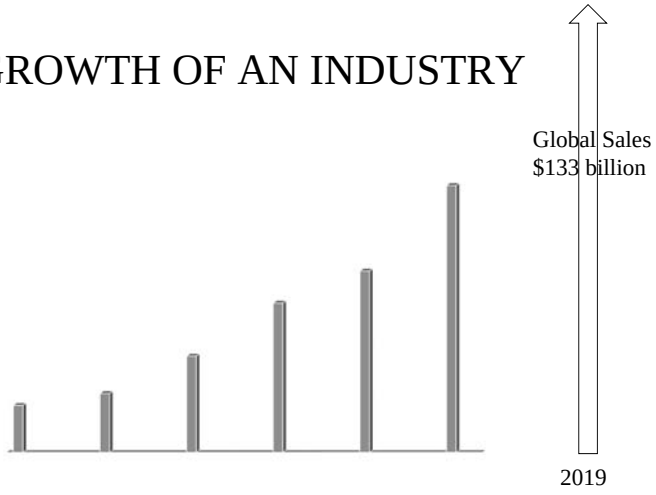
Study by the British Naval Surgeon James Lind in 1747 was one of the first nutrition clinical trials in which 12 sailors who had scurvy were randomly selected to receive 1 of 6 treatments (2 sailors) per treatment. Only citrus fruit worked (Vit C).

Current Trend For Supplement Use

Shift from treatment of micronutrient deficiency diseases to "prevention of and promotion of overall health and longevity"

U.S. population no longer dies from micronutrient deficiencies, but rather macronutrient excess.

GROWTH OF AN INDUSTRY



Consumer Use of Supplements

- Dissatisfaction with limitations of conventional medicine
- Perception of Western model of medicine – "Drugs" only and not "natural"
- Medical practices of other cultures
- To improve or maintain health
- Prevention issues and desire to reduce meds
- Convenience shopping and think less costly

Dietary Supplement Health and Education Act of 1994

- Congress passed into law this act which allows a supplement to be excluded from regulation as a food additive or drug.
- Dietary supplements do not have to have any research or efficacy trials to be brought to market.
- Currently >50,000 supplements on market

What is a Supplement?

- A supplement has to present in the food supply in a natural form.
- Or contain substances that have not been confirmed as being essential for life, but has a potential beneficial biological effect.
- Either extracted from food sources or synthetic
- Ingredients and dosages must be stated on the label.

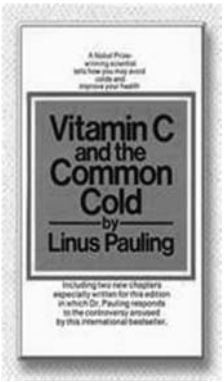
Supplement Claims

- The act allows manufacturers to make nutritional benefit claims that are not disease-related claims
- OK to make health claim as long as product or ingredients cannot prevent, treat, or cure a specific disease.

Types of Supplements That Are HYPE

Cure For The Common Cold

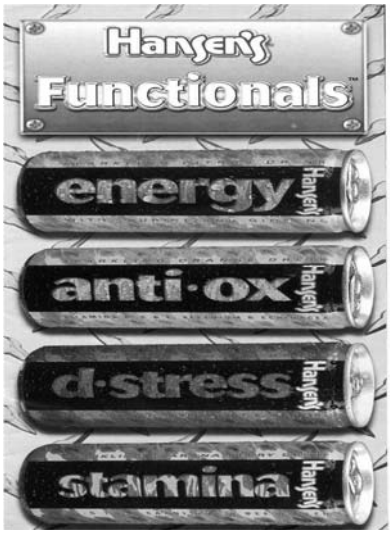
Zinc: Inconsistent evidence 2008- $24 million fraud



NEJM 2011: No effect

Echinacea

- Mechanism of action: proposed to enhance immune system, unclear mechanism.
- Echinacea has traditionally been used to treat or prevent colds, flu, and URI but 2 recent NCCAM-funded studies showed no effect.
- Adverse Event: In patient with asthma, had anaphylaxis (a life-threatening allergic reaction).



Valerian Root

- **Therapeutic use:** Described by Hippocrates to treat patients for insomnia and anxiety.
- Favorable data were from studies with small sample sizes, used different amounts and sources of valerian, and high participant withdrawal rates
- Recent randomized controlled trials do not support benefit.

Examples of Weight Loss Ads

False Claim

- Claim: Lose weight while you sleep.
- Fact: Products and programs that promise quick easy weight loss are bogus. To lose weight, you have to lower your intake of calories and increase your physical activity.

False Claim

- Lose 12 pounds in 2 days, or lose 30 ponds in 30 days
- Fact: The faster you lose weight, the more muscle you lose and lower basal metabolic rate. Healthy weight loss rec is 1 pound per week

Healthy Water?

Vitaminwater

- Coca Cola bought VW for $4.1 billion in 2004
- 2009: Class-action that the marketing of the drink as a "healthful alternative" to water is deceptive and in violation of FTC
- “33 grams of sugar in each bottle do more to promote obesity, diabetes and other health problems than the vitamins in the drinks do to perform the advertised benefits listed on the bottles".
- Coca Cola had to change label removing that VW was a healthy alternative to water

Types of Supplements That May HARM

Formula-One: The Ultimate Supplement

- "all natural supplement that will make you feel better and have more energy"
- "control of hunger, reduced sugar cravings, burn more fat and lose weight"
- Contains boron, chromium, Vitamins B3, C and E, multiple herbs including Ma-huang (ephedrine), Kola Nut (caffeine), White Willow Bark (salicylate), Gingko Biloba (aspirin + Vit E), Bladderwrack (iodine).

FDA Pulls Formula One

- Affiliated Consultants International instructed to stop marketing this product due to numerous adverse events and fatalities associated with this product.
- Class action law suit against company.

Interactions of Supplements and Medications ?

We know about drug/nutrient interactions and drug/drug interactions. Now there is the supplement/drug interactions.

Specific Supplement Interactions

- **Ginkgo** Biloba:
- Mechanism of action: antioxidant like Vitamin E and antiplatelet effect like aspirin.
- Interaction: with anti-coagulant medications such as Aspirin, Coumadin (Warfarin), Heparin.
- Adverse Event: Multiple cases of spontaneous hemorrhage (GI, Brain)

Adulteration

- The U.S. GAO received 6307 reports of health problems from 2008-2011 associated with supplements.
- 92% of tested herbal supplements contained lead or other chemical contaminants.
- Protein powders tested found unsafe levels of arsenic, cadmium, lead and mercury.
- Study between 2007-2016 identified 776 products containing unlisted pharmaceutical drugs (86% were marketed for weight loss and sexual performance and contained sildenafil)

Supplement Studies on Product Purity

- 50% of dietary supplements tested had mislabeled ingredients (FTC, 2000)
- 25% of sports supplements tested were contaminated with "banned" substances (USADA, Jan 2010)
- FTC trying to enforce supplement labels and content with USP (US Pharmacopoeia) which means product passed tests for purity.

FTC Releases Report on Dietary Supplement Advertising

- Report shows 55% false claims and another 40 % misleading or deceptive ads.
- Two major trends in past 10 years:

  1) For weight loss, shift away from exercise to taking the diet pill only to lose weight.

  2) New ads much more likely to make misleading and deceptive promises.

SAFETY BURDEN: Report Problems

Adverse effects with dietary supplements should be reported to FDA as soon as possible. If your patient experiences an adverse effect, report this problem to FDA.

For information on how to report, go to www.fda.gov/FDAgov/Food/DietarySupplements/Alerts/ucm111110.htm.

Types of Supplements That HELP

Dietary Supplement Fact Sheet: Vitamin D

NIH Office of Dietary Supplements:

Vitamin D is a fat-soluble vitamin naturally present in very few foods (cod liver oil) and produced endogenously when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis

Vitamin D (+ Calcium) helps protect adults from osteoporosis.

Serum concentration of 25(OH)D best indicator of vitamin D status.

VIT D – Super Hormone?

4 fold increase in sales in past decade

Emerging epidemiologic data suggest that vitamin D has a protective effect against colon cancer, but not as strong against prostate and breast cancer, and are variable for cancers at other sites.

50 trials underway with Vit D and CVD, Cancer, SADS

The FDA approved Qualified Health Claims (QHC's) for Vit D and calcium supplementation to reduce the risk of osteoporosis by reducing bone loss.

QHC's are supported by scientific evidence and given by FDA to be able to make disease related claim on marketing and advertising.

Natural Anti-inflammatory Foods and Supplements

- **Omega-3 EFA:** fastest growing (10 fold in past decade)
- Source: Marine and plant oils (fish oil, flax seed). Wild elk has same amount as wild salmon.
- Active ingredients: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) enhance conversion of COX to prostaglandin E3 (PE3).
- PE3 inhibits arachidonic acid conversion to PE2 (highly inflammatory).

Anti-inflammatory Supplements

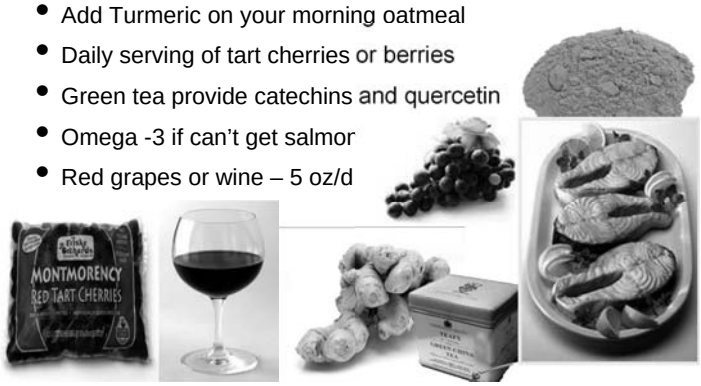
- **Curcumin**
- Source: Tumeric comes from flowering plant in the ginger family.
- Human mechanism: inhibits both Cox-1 and Cox-2 inflammatory pathways.
- Alternative to NSAIDS but may have same GI side effects. Not to be taken with NSAIDS.

Anti-inflammatory Supplement

- **Resveratrol**
- Sources: Japanese knotweed and grapes (skin)
- Role is to protect the plant from infection and UV radiation
- Anti-inflammatory Mechanism: inhibits TNF – alpha and IL-1.
- NIH Human Cancer Trials: melanoma, colon cancer

Anti-Inflammatory Diet

- Add in Ginger sprinkled on trail mix
- Add Turmeric on your morning oatmeal
- Daily serving of tart cherries or berries
- Green tea provide catechins and quercetin
- Omega -3 if can't get salmor
- Red grapes or wine – 5 oz/d



Coenzyme Q10

It is required for the conversion of substrate in the mitochondria to produce ATP

A study published in 2007 in "Otolaryngology -- Head and Neck Surgery" found that coenzyme Q10 at a dosage of 100 mg three times per day for 16 weeks significantly improved symptoms of tinnitus in patients with low levels of CoQ10.

Current large NIH intervention study underway looking at co-Q10 on tinnitus.

A 2018 meta-analysis concluded that there was evidence for oral CoQ_{10} at 200 mg daily in reducing statin-associated myopathy (muscle pain and weakness)

Metabolic Myopathy Treatment – No cure

Acetyl L-carnitine 500 mg/d
Coenzyme Q-10 300mg/d
Vitamin E 400IU/d
B-complex to include folate, riboflavin and cyanocobalamin
Selenium 50mcg/d
Alpha-lipoic acid 300mg/d
L-Arginine 2 grams TID
Vit A 5000 iu per day

Amino Acid Supplementation Mitigates Muscle Atrophy After TKA

- Dreyer H, Owen E, Kuehl K et al. Journal of Bone and Joint Surgery. June 4, 2018
- Findings: twice daily ingestion of 20 g of EAA starting 1 week prior to and for 6 wks after TKA preserved LBM significantly greater than placebo.
- In older adults undergoing major surgery, EAA supplementation is beneficial to reduce muscle loss during and after recovery.

ANTIOXIDANTS and CANCER

- Mechanism of action: inhibit oxidant formation, interfere with the oxidant activity once already formed, and repair injury caused by oxidants.
- Findings from epidemiologic data show no benefit from antioxidants in prevention of cancer, but clinical trials do show some benefit.

Randomized Trials of Antioxidant Supplements on Cancer and CVD

TRIAL	Subject #	TREATMENT	EFFECT
-Linxian (Dysplasia)	4000	Multivit	0
-Linxian (General)	30000	E/BC/Selenium	+
-ATBC	29000	E/BC	--
-CARET	18000	BC/A	0
-PHS	22000	BC	--
-NHS (CHD)	88000	Folate/B6	+
-CHAOS (CHD)	2100	E	+, 0
-Northern Skin CA	1900	BC	0
-Southern Skin CA	1300	Selenium	+

0 = no effect
+ = effect, -- = adverse effect

Antioxidants and CHD

- "Antioxidant supplements have not been proven to prevent heart disease by current clinical and epidemiological evidence (2010 Surgeon General)
- USPSTF -2015. Evidence does support taking supplements for disease prevention including Mvit

Antioxidants: Cancer and CHD Prevention Recommendation

Obtain antioxidants from food

Fruits and vegetables derive antioxidant properties from the chemical that causes their various colors

Red - tomato, red plum, watermelon, pink grapefruit. Lycopene inhibit cancer cell growth.

Red/Purple - grapes, cherries, strawberries, raspberries, blueberries, prunes, red apples. Proanthocyanins inhibit cancer cell growth.

Green - broccoli, brussel sprouts, cabbage, bok choy. Isothio-cyanates increase liver proteins against carcinogens.

Green/Yellow - spinach, corn, kale, avocado, mustard greens. Lutein protects vision, the heart, and inhibits cancer cell growth.

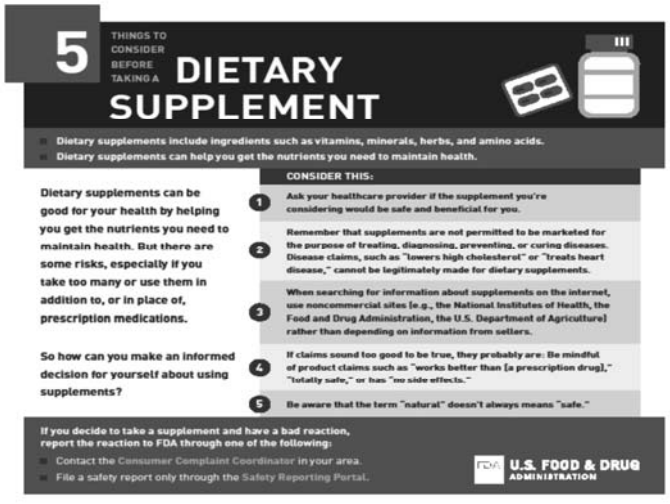
Orange - carrots, cantaloupe, pumpkin, apricots. Beta carotene (vision/immune fxn).

Orange/Yellow - oranges, lemons, papaya, peaches, nectarines, pineapple. Flavonoids inhibit tumor growth and repair DNA. Limonoids in the skin of oranges and lemon inhibit tumor growth.

Green/White - Garlic, onion, celery, chives, pears, leeks. Allyl sulfides inhibit tumor cell.

CONCLUSION

- Since DSHEA, explosion in nutritional supplement industry.
- Healthy people buying and taking supplements.
- Use must be guided by scientific study of efficacy, minimum and maximum safety doses, interactions, adverse effects, and costs.



Insomnia

OHSU Internal Medicine Review
April 11, 2019

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Portland, OR
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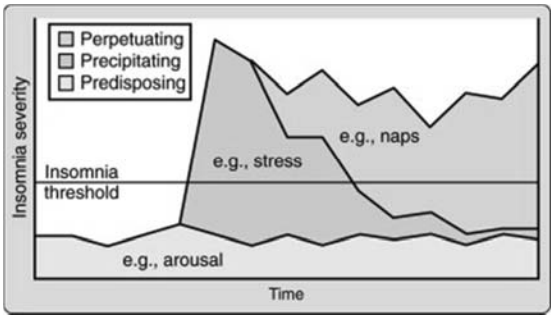
Insomnia

- Definitions
- Etiology
- Morbidity/Co-Morbidity
- Diagnosis
- Treatment
  - Pharmacologic
  - Behavioral
- Case

Definitions: DSM-V

- Insomnia Disorder (307.42)
- Dissatisfaction with the amount or quality of sleep along with:
  - Difficulty falling asleep
  - Difficulty staying asleep
  - Early-morning awakening
- "Causes clinically significant distress or impairment"
- Happens at least 3 nights per week
- Has lasted at least 3 months
- Not better or adequately explained by:
  - Inadequate opportunity for sleep
  - Another sleep disorder (e.g., sleep apnea, narcolepsy or a circadian rhythm sleep disorder)
  - Substance use
  - Other mental or medical disorders

Etiology



From: Kryger, Roth, Dement, eds., Principles and Practice of Sleep Medicine, 2011
Also see: Reimann et al. Sleep Med Rev 2010;14: 19-31

Etiology: Evidence for physiological hyperarousal

- Hyperarousal ← → Insomnia?
- Genetic component? Higher monozygotic twin concordance
- Insomiacs don't show evidence of sleep deprivation on multiple sleep latency test (MSLT, nap study)
- Increased high frequency EEG in non-REM sleep
- Increased metabolic rate (sleep & wake)
- Increased cortisol levels
- Increased sympathetic/decreased parasympathetic activity during sleep (HRV)

Reimann et al. Sleep Med Rev 2010;14: 19-31
Bonnet and Arand Sleep Med Rev 2010;14: 9-15

Morbidity/Co-Morbidity

- Psychiatric: *prevalence* of any psychiatric disorder is 2-3x greater in insomniacs, depression *prevalence* is 4x greater
- Decreased quality of life
- Increased accidents and decreased productivity
- Increased *risk* of:
  - Hypertension
  - Diabetes
  - Metabolic syndrome ($\geq$ 3: hyperglycemia, hypertriglyceridemia, increased waist circumference, HTN)
  - Myocardial infarction
  - Depression

Roth T, Journal of Clinical Sleep Medicine 2007; 3:S7-S10.
Vgontzas et al., Sleep 2009; 32: 491-497.
Vgontzas et al., Diabetes Care 2009; 32:1980-1985.
Troxel et al., Sleep 2010; 33: 1633-1640.
Laugsand et al., Circulation 2011; 124: 2073-2081
Laugsand et al., Euro Heart J 2013; 124: 2073-2081
Breslau N, Biol Psychiatry 1996;39:411-418
Chang PP, Am J Epidemiol 1997;146:105-114
Weissman MM, Gen Hosp Psych 1997;19:245-250

Morbidity/Co-Morbidity: Depression

Table 3. First onset of a psychiatric disorder over the subsequent year in individuals with insomnia and no psychiatric disorder as compared with individuals with neither

	At first interview			
	Insomnia and no psychiatric disorder	No insomnia and no psychiatric disorder		
Number at risk	414	4826	Odds ratio[a]	95% CI
First onset in following year	Rate/100			
Major depression	2.7	0.5	5.4*	2.6–11.3
Panic disorder	1.0	0.1	20.3*	4.4–93.8
Obsessive-compulsive disorder	1.6	0.7	2.2	0.9–5.1
Alcohol abuse	3.3	1.8	2.3*	1.2–4.3
Drug abuse	0.6	0.3	1.9	0.5–7.2

CI = confidence interval.
[a] Odds ratio adjusted by age, sex, and site.
* $p < 0.05$.

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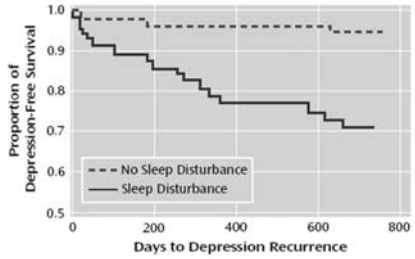
Weissman MM, Gen Hosp Psych. 1997;19:245-250.

Morbidity/Co-Morbidity: Depression

FIGURE 1. Time to Depression for Older Adults With a Prior Depression History According to Sleep Disturbance at Baseline



Cho HJ, Am J Psych. 2008;165: 1543-1550.

Morbidity/Co-Morbidity: Hypertension

Table 2—Multivariable Adjusted Odds Ratio (95% CI) of Hypertension and Insomnia or Objective Sleep Duration

Sleep Difficulty	Model 1			Model 2			Model 3		
	Odds Ratio	95%	CI	Odds Ratio	95%	CI	Odds Ratio	95%	CI
Normal sleeping	1.00			1.00			1.00		
Poor sleep	1.30	0.98	1.72	1.25	0.94	1.70	1.23	0.92	1.65
Insomnia	2.76	1.82	4.20	2.55	1.66	3.90	2.41	1.57	3.70
Sleep duration									
> 6 h	1.00			1.00					
5–6 h	1.19	0.89	1.58	1.18	0.88	1.57	1.13	0.85	1.51
≤ 5 h	1.65	1.22	2.23	1.65	1.22	2.23	1.56	1.14	2.11

Model 1. Adjusted for age, race, sex, BMI, diabetes, and sampling weight.
Model 2. Adjusted for age, race, sex, BMI, diabetes, smoking status, alcohol consumption, depression, SDB, and sampling weight.
Model 3. Adjusted for age, race, sex, BMI, diabetes, smoking status, alcohol consumption, depression, SDB, and sampling weight and objective sleep duration (or insomnia). The interaction between insomnia and objective sleep duration is statistically significant, $P < 0.05$.

Measurements: *Insomnia* was defined by a complaint of insomnia with a duration ≥ 1 year, while *poor sleep* was defined as a complaint of difficulty falling asleep, staying asleep, or early final awakening.

Vgontzas et al., Sleep 2009; 32: 491-497.

Morbidity/Co-Morbidity: Hypertension

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Morbidity/Co-Morbidity: Hypertension

Table 3—Multivariable Adjusted Odds Ratio (95% CI) of Hypertension Associated with Insomnia and Objective Sleep Duration

Sleep difficulty	Sleep duration	Sample size	Adjusted OR	95% CI	
				Low	Upper
Normal sleeping	> 6 h	527	1.00		
Poor sleep	> 6 h	249	0.79	0.52	1.20
Insomnia	> 6 h	86	1.31	0.70	2.46
Normal sleeping	5-6 h	235	0.86	0.60	1.22
Poor sleep	5-6 h	146	1.48	0.90	2.42
Insomnia	5-6 h	49	3.53	1.57	7.91
Normal sleeping	< 5 h	260	1.13	0.79	1.62
Poor sleep	< 5 h	125	2.43	1.36	4.33
Insomnia	< 5 h	64	5.12	2.22	11.79

All data adjusted for age, race, sex, BMI, diabetes, smoking status, alcohol consumption, depression, SDB, and sampling weight.
The interaction between insomnia and objective sleep duration is statistically significant, $P < 0.01$.
Compared to the common reference group, persons without insomnia/ poor sleep and slept more than 6 hours.

Vgontzas et al., Sleep 2009; 32: 491-497.

Morbidity/Co-Morbidity: Hypertension

Table 3—Multivariable Adjusted Odds Ratio (95% CI) of Hypertension Associated with Insomnia and Objective Sleep Duration

Sleep difficulty	Sleep duration	Sample size	Adjusted OR	95% CI	
				Low	Upper
Normal sleeping	> 6 h	527	1.00		
Poor sleep	> 6 h	249	0.79	0.52	1.20
Insomnia	> 6 h	86	1.31	0.70	2.46
Normal sleeping	5-6 h	235	0.86	0.60	1.22
Poor sleep	5-6 h	146	1.48	0.90	2.42
Insomnia	5-6 h	49	3.53	1.57	7.91
Normal sleeping	< 5 h	260	1.13	0.79	1.62
Poor sleep	< 5 h	125	2.43	1.36	4.33
Insomnia	< 5 h	64	5.12	2.22	11.79

All data adjusted for age, race, sex, BMI, diabetes, smoking status, alcohol consumption, depression, SDB, and sampling weight.
The interaction between insomnia and objective sleep duration is statistically significant, $P < 0.01$.
Compared to the common reference group, persons without insomnia/ poor sleep and slept more than 6 hours.

Vgontzas et al., Sleep 2009; 32: 491-497.

Morbidity/Co-Morbidity: Hypertension

Table 3—Multivariable Adjusted Odds Ratio (95% CI) of Hypertension Associated with Insomnia and Objective Sleep Duration

Sleep difficulty	Sleep duration	Sample size	Adjusted OR	95% CI	
				Low	Upper
Normal sleeping	> 6 h	527	1.00		
Poor sleep	> 6 h	249	0.79	0.52	1.20
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The interaction between insomnia and objective sleep duration is statistically significant, $P < 0.01$.
Compared to the common reference group, persons without insomnia/ poor sleep and slept more than 6 hours.

Vgontzas et al., Sleep 2009; 32: 491-497.

Diagnosis

Diagnosis

- Made on the basis of diagnostic criteria
- Overnight sleep study only indicated for the diagnosis of *another sleep disorder* (e.g., sleep apnea or periodic limb movement disorder)
- What is useful? **History/ROS, questionnaires, sleep diaries** and wrist actigraphy
- Difficult in practice to differentiate between what were once called “primary” and “secondary” insomnias

Diagnosis

- History of the Insomnia
  - When did it begin?
  - Any known precipitants?
  - Usual questions:
    - Timing (number of episodes & frequency)
    - Duration
    - Severity (e.g., ISI questionnaire),
    - Any known modifying factors (e.g., stress or pain)?

Diagnosis

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?
Very Satisfied (0) Satisfied (1) Moderately Satisfied (2) Dissatisfied (3) Very Dissatisfied (4)

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?
Not at all Noticeable (0) A Little (1) Somewhat (2) Much (3) Very Much Noticeable (4)

6. How WORRIED/DISTRESSED are you about your current sleep problem?
Not at all Worried (0) A Little (1) Somewhat (2) Much (3) Very Much Worried (4)

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?
Not at all Interfering (0) A Little (1) Somewhat (2) Much (3) Very Much Interfering (4)

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0-7 = No clinically significant insomnia
8-14 = Subthreshold insomnia
15-21 = Clinical insomnia (moderate severity)
22-28 = Clinical insomnia (severe)

Used via courtesy of www.myhealth.va.gov with permission from Charles M. Morin, Ph.D., Universite Laval

Diagnosis

- Characterizing the Insomnia
  - Routine prior to trying to go to sleep
  - **Range** of bedtimes and wake times (including days off)
  - Bedtime routine (e.g., lights out right away?)
  - How long does it take to fall asleep, number & duration of awakenings, duration of sleep, duration of time in bed
    - Sleep latency
    - Wake after sleep onset (WASO)
    - Total Sleep Time (TST)
    - Sleep Efficiency (SE) = percentage of sleep opportunity that is sleep
  - What do they do when awake (e.g., stay in bed?)

Diagnosis

- Characterizing the Insomnia (cont.)
  - Excessive mental activity? Worry or sadness (even if they don't meet GAD or MDD criteria)?
  - Worry about sleep itself? Excessive efforts to fall asleep?
  - Any problems with noise, temperature, light or safety?
  - Does pain or tinnitus disturb sleep?
  - Do they nap? Can they nap? Do they try to catch up on sleep after a bad night?
  - Do they ever sleep well (e.g., away from their usual environment)?

Diagnosis

- Sleep ROS:
  - Snoring, witnessed apneas, choking/gasping, reflux, nocturia, morning headaches, morning dry mouth, daytime somnolence, or napping? - Sleep Apnea
  - Nightmares? Dream enactment? – PTSD vs trauma associated sleep disorder vs REM Behavior disorder
  - Bruxism?
  - Sleepwalking or sleep talking? - Slow-wave sleep parasomnias
  - *"Do you have a restless, nervous, tingly, or creepy-crawly feeling in your legs that disrupts your ability to fall or stay asleep?"* - Restless Legs Syndrome
  - Kicking or twitching during sleep? - Periodic Limb Movement Disorder
  - Sleep paralysis, hypnogognic/hypnopomic hallucinations, cataplexy, & daytime somnolence? - Narcolepsy

Diagnosis

- The history or characterization of insomnia as well as the sleep ROS may seem obvious
- However, they impact treatment even if there isn't complete diagnostic clarity

Treatment

Treatment

- Treat underlying Medical or Psychiatric Condition (insomnia symptoms can remain)
- Improve sleep hygiene (limited data on efficacy)
- Change environment
- Cognitive-Behavioral Therapy for Insomnia (CBT-I)
- Pharmacologic
- Light and melatonin (“chronotherapy”)

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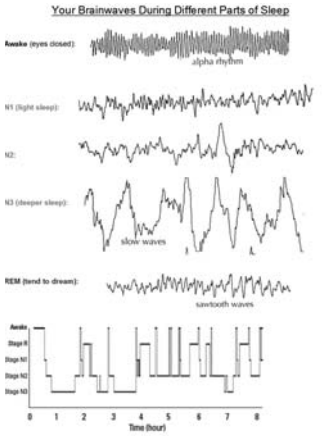
Treatment: Patient Education

Treatment: Patient Education

- Sleep is a dynamic & active process
- Different parts (stages) of sleep based on the EEG
- The concept of local sleep

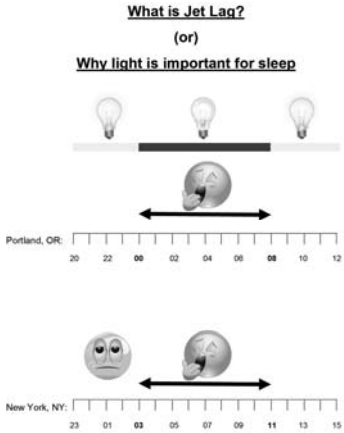


Vyazovsky et al., Nature 2011; 472: 443-447
Nobili et al., Prog Brain Res 2012; 199: 219-232

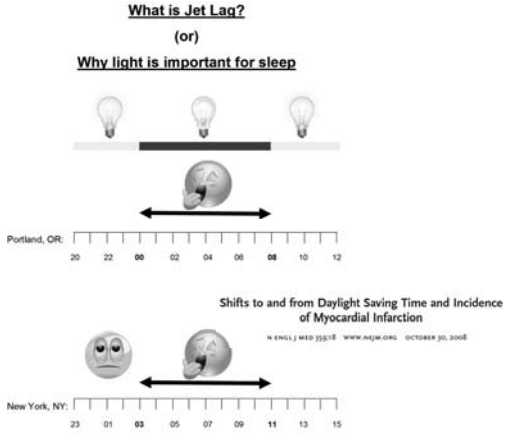
Treatment: Patient Education

- There are multiple areas in the brain involved in generating sleep & wakefulness
- The “two-process” model of sleep: the 24-hour body clock and homeostatic sleep drive

Treatment: Patient Education

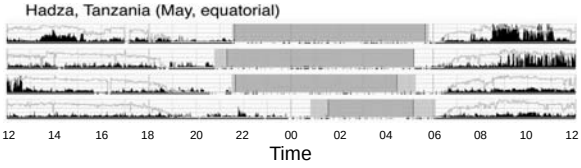


Treatment: Patient Education



Treatment: Patient Education

Sleep in hunter-gatherers

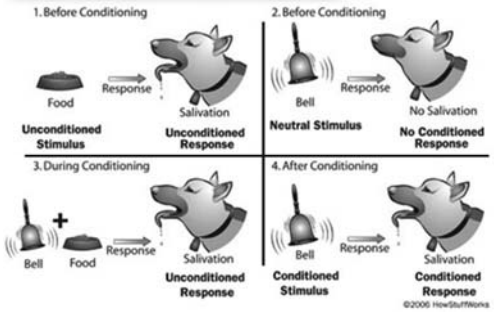


Black = when they were moving
Red = awake
Yellow = light level
Dark Blue = main sleep period

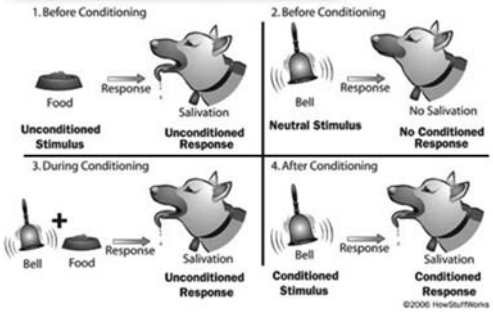
Yetish et al., Curr Biol. 2015;25: 1-7

- Sleep under “natural” light/dark conditions
- Cultural ideas about sleep

Treatment: Patient Education



Treatment: Patient Education

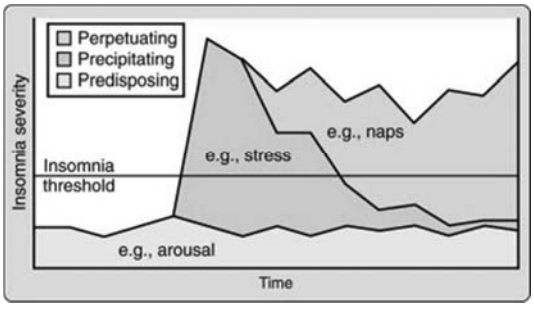


Resetting of the circadian clock by a conditioned stimulus

Shimon Amir & Jane Stewart

NATURE · VOL 379 · 8 FEBRUARY 1996

Treatment: Patient Education



From: Kryger, Roth, Dement, eds., Principles and Practice of Sleep Medicine, 2011

Treatment

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Treatment: Pharmacologic

Table 3. Medications Commonly Used for Insomnia.

Medication	Dose in Adults		Half-Life	Most Common Side Effects
	<65 yr of age	≥65 yr of age		
Antihistamines	mg		hr	
Benzodiazepine-receptor agonists				Daytime sedation, ataxia, anterograde amnesia, complex sleep-related behaviors (e.g., sleepwalking)
Temazepam (Restoril)*	7.5–30	7.5–15	8–10	
Lorazepam (Ativan)	0.5–2	0.5–1	8–12	
Eszopiclone (Lunesta)*	2–3	1–2	6–9	Unpleasant taste†
Zolpidem (Ambien)*	5–10	2.5–5	2.5	
Triazolam (Halcion)*	0.125–0.5	0.125–0.25	2.5	
Zaleplon (Sonata)*	5–20	5–10	1	
Antidepressants				
Trazodone (Desyrel)	25–100	25–100	6–8	Daytime sedation, orthostasis
Mirtazapine (Remeron)	7.5–30	7.5–30	20–30	Daytime sedation, anticholinergic effects, weight gain
Doxepin (Sinequan, Silenor)*	10–50 (3–6 approved)	10–50	12–18	Daytime sedation, anticholinergic effects, weight gain (not at approved doses)
Orexin antagonist: suvorexant (Belsomra)*	10–20	10–20	9–13	Daytime sedation
Melatonin agonist: ramelteon (Rozerem)*	8	8	1	Daytime sedation
Anticonvulsant: gabapentin (Neurontin)	100–900	100–900	5–9	Daytime sedation, dizziness, weight gain

Winkleman NEJM 2015;373:1437-1444
More detailed review: Buysee JAMA 2013;309: 706-716

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Treatment: Behavioral

- Progressive relaxation
- EMG biofeedback
- Guided imagery
- Stimulus control therapy: in bed only when sleepy, bed/bedroom is for sleep and sex only, & get out of bed when unable to sleep
- Bed Restriction: fixed waketime, change bedtime by 15 minutes if sleep efficiency >90% in the last week
- Regular sleep schedule and light/dark schedule
- Requires the use of a sleep diary

Morin CM, et al. Sleep 2006;29:1398-1414

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- Requires the use of a sleep diary

Morin CM, et al. Sleep 2006;29:1398-1414

Treatment: Behavioral

Table 1. Cognitive-Behavioral Interventions for Insomnia[a]

Intervention	General Description	Specific Techniques
Sleep hygiene education	Recommendations promoting behaviors that help sleep, discouraging behaviors that interfere with sleep	Do not try to sleep. Avoid stimulants (caffeine, nicotine). Limit alcohol intake. Maintain a regular sleep schedule 7 nights per wk. Avoid naps. Get regular exercise at least 6 h prior to sleep. Keep the bedroom dark and quiet.
Stimulus control	Based on operant and classical conditioning principles: nonsleep activities and the bedroom environment can serve as stimuli that interfere with sleep. Treatment prescribes behaviors that strengthen associations between the environment and sleep.	Go to bed only when sleepy. Use the bed and bedroom for sleep only. Do not read, watch television, talk on the phone, worry, or plan activities in the bedroom. If unable to fall asleep within 10-20 min, leave the bed and the bedroom. Return only when feeling sleepy again. Set the alarm and wake up at a regular time every day. Do not use the snooze button on the alarm. Do not nap during the day.
Sleep restriction therapy	Based on experimental evidence that sleep is regulated by circadian and homeostatic processes. Treatment increases homeostatic sleep drive by reducing time in bed and maintaining a consistent wake time in the morning to reinforce circadian rhythms.	Restrict time awake in bed by setting strict bedtime and rising schedules limited to the average number of hours of actual sleep reported in 1 night. Keep a fixed wake-up time, regardless of actual sleep duration. If after 10 d sleep efficiency is lower that 85%, further restrict bedtime by 15-30 min. Increase time in bed by advancing bedtime by 15-30 min when the time spent asleep is ≥85% of time in bed.

Buysee JAMA 2013;309: 706-716

Treatment: Behavioral

Bed Restriction

1. Keep a sleep diary throughout the treatment period.
2. First work on keeping the same **lights out & lights on schedule**. Keep the same bedtimes and out-of-bed times on weekends and weekdays. Get help from family or friends in getting out of bed at the same time each day.
3. If you start with 6 hours of bed restriction, determine your starting "lights out" time by subtracting 6 hours from your chosen wake time.
4. If you are able to obtain good sleep (that is, about 90% of the time you are in bed is sleep) for three days, add on 15 minutes of time in bed. Add on the additional time in bed at the beginning of the night, keeping your wake time the same.
5. Every three days reevaluate: If you are obtaining good sleep add on another 15 minutes of time in bed. If insomnia returns, subtract 15 minutes of time in bed.
6. Make sure you get as much rest as you need during your wake/lights on time.

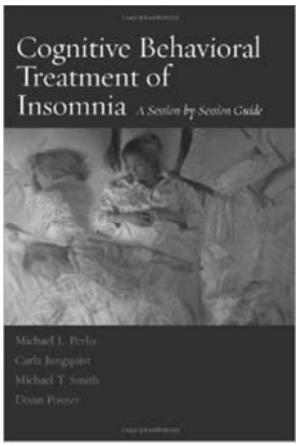
Starting Lights out/In Bed: _____

Lights On/Out of Bed: _____

Stimulus Control

1. The goal of stimulus control is to have your brain think the bed is a place to sleep instead of a place to be awake.
2. **The bed is for sleep and sex only**. Go to bed only when you are sleepy.
3. If you don't fall asleep in 15 to 20 minutes, get up, go into another room (if possible), and **lay quietly in darkness** until sleepy. This other place is your "insomnia bed." Try listening to music, a book on tape, or the radio.
4. Don't watch the clock. Just guess when 15-20 minutes have passed. Plan ahead of time what you are going to do during the time you are out of bed.

Treatment: Behavioral



Treatment: Efficacy (Pharmacologic & Behavioral)

Variable	Average Improvement (consider study length and how measured – PSG vs. diary)
Sleep Latency	~15 to 30 minutes faster
Number of Awakenings	~ one less awakening
Total Sleep Time	~20-60+ minutes more sleep

Smith MT et al., Am J Psych. 2002;159:5-11
Buysee JAMA 2013;309: 706-716
Krystal AD et al., Sleep. 2008;31:79-90.
Glass et al. J Clin Psychopharm 2008; 28: 182-188
Krystal, et al. Sleep 2010; 33:1553-61
Michelson et al. Lancet Neurol 2014; 13: 461-471
Morin CM, et al. JAMA 1999;281:991-9
Jacobs GD, et al. Arch Intern Med 2004;164:1888-1896

Treatment: Comparisons

- Similar efficacy pharmocologic vs. cognitive-behavioral treatments in several studies
- 8 weeks of CBT vs. temazepam vs. combined treatment.

Morin CM, et al. JAMA 1999;281:991-9
Jacobs GD, et al. Arch Intern Med 2004;164:1888-1896
Morin CM, et al. Sleep 2006;29:1398-1414

Treatment: Comparisons

- 8 weeks of: temazepam (7.5-30 mg, avg=20 mg), placebo, CBT-I (8x90 min.), or combination.
- Temazepam increased total sleep time by 43.7 min.
- CBT-I increased total sleep time by 30.5 min. and by 65.2 min. at 2 years
- Combo increased total sleep time by 42.2 min.
- Placebo increased total sleep time by 19.7 min.

Table 2. Group Means and Number of Subjects in Each Treatment Condition*

Assessment Modes	CBT	PCT	Combined	Placebo
		Total Sleep Time		
Sleep diary				
Pretreatment	321.50 (79.8)	340.21 (73.6)	289.77 (64.7)	331.04 (59.5)
Posttreatment	352.00 (52.4)	383.90 (56.8)	331.93 (65.4)	350.70 (64.7)
3-mo Follow-up	355.57 (54.34)	373.53 (73.6)	327.75 (87.4)	370.34 (75.3)
12-mo Follow-up	375.32 (54.07)	353.52 (61.8)	317.04 (98.0)	319.75 (80.0)
24-mo Follow-up	386.70 (63.41)	351.73 (60.1)	330.63 (85.6)	330.53 (116.0)
Polysomnography				
Pretreatment	353.90 (43.8)	342.90 (51.0)	346.90 (45.8)	371.00 (50.1)
Posttreatment	360.70 (34.4)	378.20 (46.3)	356.10 (38.0)	373.80 (49.5)

*CBT indicates cognitive-behavior therapy; PCT, pharmacotherapy. All data are mean (SD). Numbers following parentheses are number of subjects in the group.

Morin CM, et al. JAMA 1999;281:991-9

Treatment: Comparisons

TABLE 2. Efficacy of Pharmacotherapy Compared With Behavioral Therapy in 21 Studies of Persistent Insomnia

Subjective Sleep Outcome Measure (Based on Sleep Diary)	Pretreatment Value		Posttreatment Value		Difference Between Pretreatment and Posttreatment Means		Number of Studies	Number of Subjects	Weighted Effect Size[a]		95% CI for Difference Between Effect Sizes
	Mean	SD	Mean	SD	Value	%			Mean	SD	
Sleep latency (minutes)											0.17 to 1.04
Pharmacotherapy	48.85	29.73	34.36	26.26	−14.49	29.7	6	129	0.45	0.28	
Behavioral therapy	54.24	28.52	30.93	16.03	−23.31	43.0	12	225	1.05[b]	0.76	
Number of awakenings											−1.24 to 1.5
Pharmacotherapy	3.00	1.99	1.83	1.37	−1.17	39.0	4	108	0.97	1.00	
Behavioral therapy	2.44	1.84	1.67	1.59	−0.77	31.6	4	58	0.83	1.30	
Wake time after sleep onset (minutes)											—[c]
Pharmacotherapy	55.09	37.80	29.49	19.50	−25.60	46.5	1	17	0.89	0.29	
Behavioral therapy	68.60	40.27	30.22	23.98	−38.38	55.9	5	81	1.03	0.19	
Total sleep time (minutes)											−0.25 to 1.01
Pharmacotherapy	332.08	55.32	372.59	48.97	40.51	12.2	6	130	0.84	0.76	
Behavioral therapy	333.28	63.66	352.89	44.22	19.61	5.9	8	146	0.46	0.62	
Sleep quality rating[d]											−1.70 to 1.22
Pharmacotherapy	3.10	0.64	3.73	0.93	0.63	20.3	4	109	1.20	1.30	
Behavioral therapy	3.38	0.66	4.34	1.30	0.96	28.4	5	82	1.44	1.20	

[a] Overall weighted effect size calculated by the formula ($\Sigma[di^*N]/\Sigma[N]$), where *di* is the effect size of the individual study.
[b] Behavioral therapy showed greater reductions in sleep latency than pharmacotherapy (t=2.88, df=20.62, p=0.01, unequal variance).
[c] Confidence interval was not calculated because there was only one pharmacological study that included wake time after sleep onset.
[d] Sleep quality ratings were standardized across studies so that higher scores reflect better sleep quality.

Smith MT et al., Am J Psych. 2002;159:5-11.

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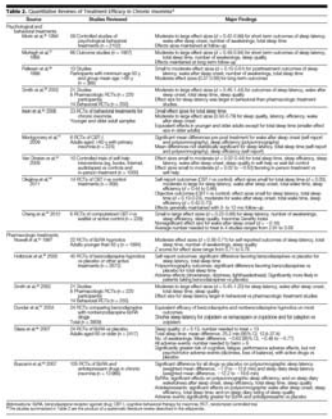
Treatment: Reviews



Buysee JAMA 2013;309: 706-716

Treatment: Hypnotic Reviews

Glass et al.[40] 2007	24 RCTs of BzRA vs placebo Adults aged 60 or older (n = 2417)	Sleep quality: *d* = 0.13, number needed to treat = 13 Total sleep time: mean difference, 25.2 min (95% CI, 12.8-37.8) No. of awakenings: Mean difference, −0.63 (95% CI, −0.48 to −0.77) All adverse events: number needed to harm = 6 Significantly greater risk of cognitive, fatigue, performance adverse effects, but not psychomotor adverse events (dizziness, loss of balance), with active drugs vs placebo
Buscemi et al.[42] 2007	105 RCTs of BzRA and antidepressant drugs in chronic insomnia (n = 13 966)	Significant difference for all drugs vs placebo on polysomnographic sleep latency (weighted mean difference, −7.0 to −12.8 min) and sleep diary sleep latency (weighted mean difference, −12.2 to −19.6 min) BzRAs: significant effects on polysomnographic sleep efficiency; and on sleep diary wakefulness after sleep onset, sleep efficiency, total sleep time, sleep quality Antidepressants: significant effects on polysomnographic wake after sleep onset, sleep efficiency, total sleep time; and on sleep diary rating of sleep quality Adverse events significantly greater for BzRA and antidepressants vs placebo

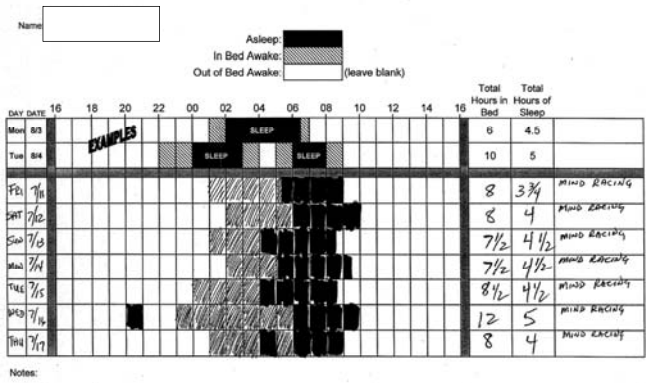
Buysee JAMA 2013;309: 706-716

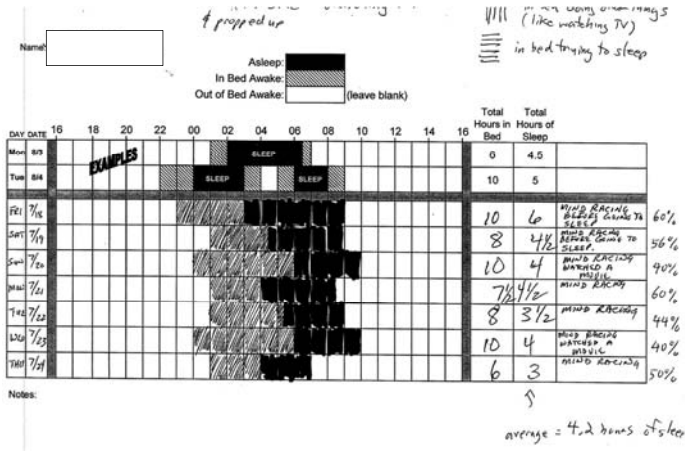
Treatment: CBT Reviews

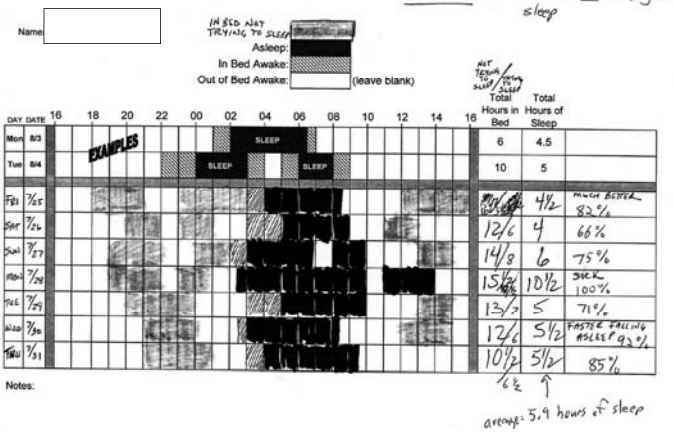
Okajima et al.[43] 2011	14 RCTs of CBT-I vs control treatments (n = 958)	Self-report outcomes (CBT-I vs control): effect sizes small for total sleep time (*d* = 0.00), moderate to large for sleep latency, wake after sleep onset, total wake time, sleep efficiency (*d* = 0.44 to 0.86) Objective outcomes (CBT-I vs control): effect sizes small for sleep latency, total sleep time (*d* = 0.13-0.24), moderate for wake after sleep onset, total wake time, sleep efficiency (*d* = 0.42-0.73) Effects generally maintained with 3- to 12-mo follow-up

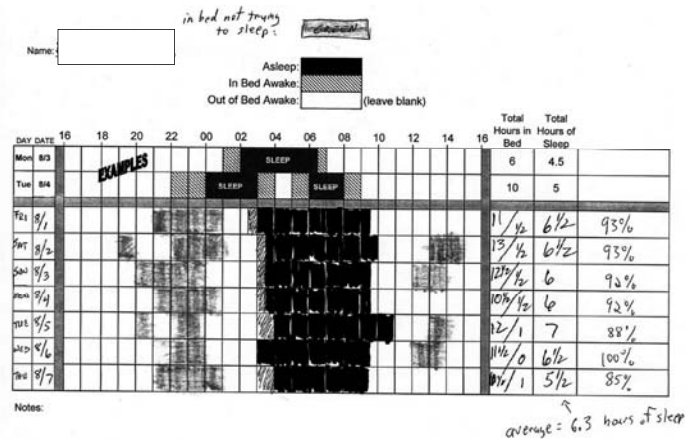
Buysee JAMA 2013;309: 706-716

Case


Name:
Asleep:
In Bed Awake:
Out of Bed Awake:
(leave blank)
DAY DATE
16 18 20 22 00 02 04 06 08 10 12 14 16
Total Hours in Bed
Total Hours of Sleep
EXAMPLES
SLEEP
SLEEP
SLEEP
Mon 8/3
Tue 8/4
6
4.5
10
5
FRI 7/11
SAT 7/12
SUN 7/13
MON 7/14
TUE 7/15
WED 7/16
THU 7/17
8
3¾
MIND RACING
8
4
MIND RACING
7½
4½
MIND RACING
7½
4½
MIND RACING
8½
4½
MIND RACING
12
5
MIND RACING
8
4
MIND RACING
Notes:


propped up
(like watching TV)
in bed trying to sleep
Name:
Asleep:
In Bed Awake:
Out of Bed Awake:
(leave blank)
DAY DATE
16 18 20 22 00 02 04 06 08 10 12 14 16
Total Hours in Bed
Total Hours of Sleep
EXAMPLES
SLEEP
SLEEP
SLEEP
Mon 8/3
Tue 8/4
0
4.5
10
5
FRI 7/15
SAT 7/19
SUN 7/20
MON 7/21
TUE 7/22
WED 7/23
THU 7/24
10
6
MIND RACING BEFORE GOING TO SLEEP
60%
8
4½
MIND RACING BEFORE GOING TO SLEEP
56%
10
4
MIND RACING WOKE UP A MIDDLE
40%
7½
4½
MIND RACING
60%
8
3½
MIND RACING
44%
10
4
MIND RACING WOKE UP A MIDDLE
40%
6
3
MIND RACING
50%
Notes:
average = 4.2 hours of sleep


3am to 9am = in bed and trying to sleep
Name:
IN BED NOT TRYING TO SLEEP
Asleep:
In Bed Awake:
Out of Bed Awake:
(leave blank)
DAY DATE
16 18 20 22 00 02 04 06 08 10 12 14 16
Total Hours in Bed
Total Hours of Sleep
EXAMPLES
SLEEP
SLEEP
SLEEP
Mon 8/3
Tue 8/4
6
4.5
10
5
FRI 7/25
SAT 7/26
SUN 7/27
MON 7/28
TUE 7/29
WED 7/30
THU 7/31
4½
MUCH BETTER
83%
12/6
4
66%
14/8
6
75%
15½
10½
SICK
100%
13/7
5
71%
12/6
5½
FASTER FALLING ASLEEP
92%
10½
5½
85%
Notes:
average = 5.9 hours of sleep


in bed not trying to sleep:
Name:
Asleep:
In Bed Awake:
Out of Bed Awake:
(leave blank)
DAY DATE
16 18 20 22 00 02 04 06 08 10 12 14 16
Total Hours in Bed
Total Hours of Sleep
EXAMPLES
SLEEP
SLEEP
SLEEP
Mon 8/3
Tue 8/4
6
4.5
10
5
FRI 8/1
SAT 8/2
SUN 8/3
MON 8/4
TUE 8/5
WED 8/6
THU 8/7
11½
6½
93%
13½
6½
93%
12½
6
92%
10½
6
92%
12/1
7
88%
11½/0
6½
100%
12½/1
5½
85%
Notes:
average = 6.3 hours of sleep

The End

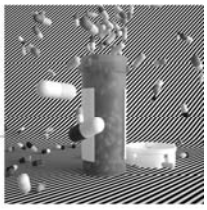
How ~~Do~~ do Drugs Work?

Craig Williams, PharmD., BCPS, FNLA
Clinical Professor, OSU/OHSU College of Pharmacy
williacr@ohsu.edu

Conflicts of interest: None

Why care about how WELL drugs work: A lot of people are on a lot of pills

New York Times, April 2017



The New York Times | https://nyti.ms/2oQXtwV

The Upshot

How Many Pills Are Too Many?

Austin Frakt

THE NEW HEALTH CARE APRIL 10, 2017

The point of prescription drugs is to help us get or feel well. Yet so many Americans take multiple medications that doctors are being encouraged to pause before prescribing and think about "deprescribing" as well.

Many patients do not handle their pill burden very well: A case study of "resistant hypertension."

Hypertension 2017;69:1113-1120

Nonadherence to Antihypertensive Treatment

Patients: n=1,348 patients referred for difficult to control BP on ≥ 3 prescribed BP medications

Methods: HPLC to detect drug in blood or urine

Risk Factors for Nonadherence to Antihypertensive Treatment

	UK	Czech Rep.
Any nonadherence	281 (41.6%)	212 (31.5%)
Partial nonadherence	183 (27.1%)	131 (19.5%)
Total nonadherence	98 (14.5%)	81 (12.1%)
Total adherence	395 (58.4%)	460 (68.5%)

So even 3 or 4 drugs can be too much for some patients to manage…

Why care how WELL drugs work? A lot of them are very expensive

US Health Care: $3.5 trillion dollar industry. Medications ~ $500,000,000,000

Public Forum; March 2019:

"Prescription Drug Pricing and Affordability"

So, understanding how well drugs work is important because:

1. We're using a lot of drugs
2. A lot of them are expensive
3. A lot of patients are having trouble with their pill burden

1. Newer anticoagulant drugs do not require monitoring and produce different outcomes when used for different clinical indications. In which of the following circumstances would you be most likely to recommend a newer anticoagulant?

   a. If it was found to provide a relative reduction in total mortality of 20%
   b. If it increased the likelihood of survival from 95% to 97%

2. New GOLD guidelines for COPD have reduced the role of inhaled steroids in favor of dual, long-acting bronchodilator therapy (LAMA+LABA). Compared to single long-acting bronchodilator therapy, which of the following accurately reflects the cost effectiveness of dual bronchodilator therapy?

   a. Compared to a single long-acting bronchodilator, dual therapy reduces a COPD hospitalization at a cost of about $100,000 per hospitalization avoided
   b. Compared to a single long-acting bronchodilator, dual therapy reduces a COPD exacerbation requiring a systemic steroid or antibiotic at a cost of about $50,000 per exacerbation avoided

Perspective
FEBRUARY 22, 2018

The Psychology of Clinical Decision Making — Implications for Medication Use

Jerry Avorn, M.D.

NEJM, February 22nd 2018

OSU Oregon State University College of Pharmacy

"Medications do not work in patients who do not take them."

C. Everett Koop, MD
Former Surgeon General of the United States

OSU Oregon State University College of Pharmacy

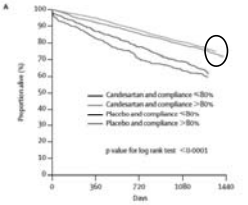
only
"Medications ~~do not~~ work in patients who do ~~not~~ take them."

C. Everett Koop, MD
Former Surgeon General of the United States

Even placebos work better in those who take them….

Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial

Brad B Granger, Karl Swedberg, Inger Ekman, Christopher B Granger, Bertil Olofsson, John J V McMurray, Salim Yusuf, Eric L Michelson, Marc A Pfeffer, for the CHARM investigators



Good adherence to placebo reduced mortality compared to poor adherence to ARB

Adherence to the ARB was barely better than adherence to placebo

Interpretation Good adherence to medication is associated with a lower risk of death than poor adherence in patients with CHF, irrespective of assigned treatment. This finding suggests that adherence is a marker for adherence to

Many drugs with small yet statistically significant benefits form the backbone of national guidelines. How effective are these drugs?

ACEI and ARB therapy for kidney protection

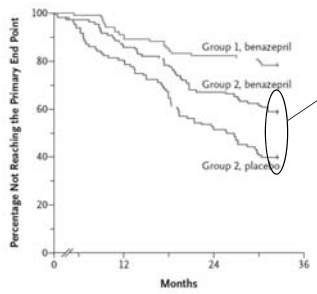
A patient who had been on ACE-I therapy presents to clinic one week after being treated in the E.D. for a potassium concentration of 6.3 mEq/L with ECG changes. The ACE-I has been held for past week and in clinic, the blood pressure is at goal (on a CCB) and you must now decide whether to re-start ACE-I therapy for nephroprotection.

In which of the following patients are you more likely to recommend resumption of ACE-I (if equal in both, OK to indicate both)?

a. A 42 year old with T1DM and an A1C of 8.5% but no nephropathy
b. A 42 year old without DM and a S_{cr} of 3.5 mg/dL

Drugs are generally very inefficient at preventing disease as compared to treating disease

ACE-I/ARB therapy treats nephropathy. The worse any disease, the lower the NNT to avoid a bad outcome. ACE-I for progression to ESRD:



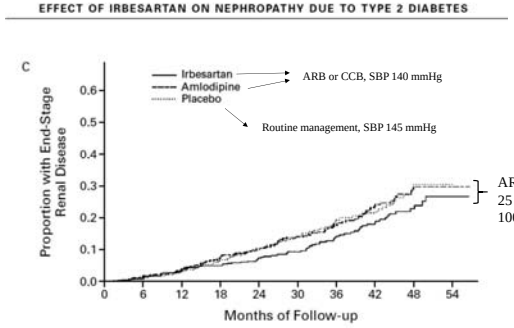
Group 1: baseline Scr 1.5-3.0 mg/dL
Group 2: Scr 3.0-5.0 mg/dL

ARR about 20% at 3-yrs for NNT ~ 5

Primary End Point: ESRD or death (but there was only 1 death in the trial)

NEJM 2006;354:131-40

IDNT trial: NEJM Sept, 2001: High risk patients with diabetic, hypertensive CKD and baseline Scr 1.7 mg/dL



ARR~ 4%, NNT ~ 25 over 4 years or 100 patients per year

From the standpoint of magnitude: Less disease = Less benefit from pharmacotherapy and a greater NNT to avoid a clinically important outcome.

For ACE-I/ARB therapy for nephroprotection (avoiding ESRD):

1. NNT = 5 over 3 years with Scr 3.5 mg/dL
2. NNT = 25 over 4 years with Scr 1.7 mg/dL (1/6 the benefit)

A patient who had been on ACE-I therapy presents to clinic one week after being treated in the E.D. for a potassium concentration of 6.3 mEq/L with ECG changes. The ACE-I has been held for past week and in clinic, the blood pressure is at goal (on a CCB) and you must now decide whether to re-start ACE-I therapy for nephroprotection.

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b. A 42 year old without DM and a S_{cr} of 3.5 mg/dL

ORIGINAL ARTICLE

N Engl J Med 2009;361:40-51

Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes

Michael Mauer, M.D., Bernard Zinman, M.D., Robert Gardiner, M.D., Samy Suissa, Ph.D., Alan Sinaiko, M.D., Trudy Strand, R.N., Keith Drummond, M.D., Sandra Donnelly, M.D., Paul Goodyer, M.D., Marie Claire Gubler, M.D., and Ronald Klein, M.D., M.P.H.

Over 5 years of follow-up, there were no cases of elevated Scr and no benefit in terms of onset of proteinuria (trend went the wrong direction for losartan)

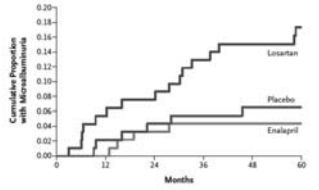

Figure 2. Kaplan–Meier Estimates of Time to Microalbuminuria.

A patient who had been on ACE-I therapy presents to the Family Medicine clinic one week after being treated in the E.D. for a potassium concentration of 6.3 mEq/L with peaked t waves. In clinic, the blood pressure is at goal on a CCB and you must now decide whether to re-start ACE-I therapy.

In which of the following patients are you more likely to recommend resumption of ACE-I (if equal in both, OK to indicate both)?

a. A 42 year old with T1DM and an A1C of 8.5% but no nephropathy
b. A 42 year old without DM and a S_{cr} of 3.5 mg/dL

In any discussion of risks vs. benefits of resuming ACE-I in these patients, a case cannot be made for a. whereas a fairly compelling case still exists for b.

1. Newer anticoagulant drugs do not require monitoring and produce different outcomes when used for different clinical indications. In which of the following circumstances would you be most likely to recommend a newer anticoagulant?

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Anticoagulation and Clinical Outcomes……..The DOACs

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The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn,

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66–0.86)	<0.001	0.90 (0.79–1.03)	0.12
Secondary outcomes‡							
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	397 (4.4)	450 (4.9)	0.72 (0.63–0.83)	<0.001	0.88 (0.77–1.01)	0.06
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	453 (5.0)	516 (5.7)	0.74 (0.65–0.85)	<0.001	0.88 (0.77–0.99)	0.04
Death from any cause	313 (3.4)	366 (4.0)	378 (4.1)	0.82 (0.71–0.96)	0.01	0.97 (0.84–1.12)	0.67

Rivaroxaban increased the likelihood of survival from 95.9% to 96.6%

18% RRR

But maybe "death" by itself is not a fair outcome for DOACs since they also reduce MI and stroke in patients with CVD.
While that is a good point, remember that DOACs also have serious side effects

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice

So maybe fair to come up with a composite outcome that takes into account major benefits beyond just survival but also accounts for the risks of serious bleeding….

If we take into account CVD events along with death and factor in fatal and major clinical bleeding:

Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)

The RRR is now exactly 20%

Likelihood of remaining event free increases from 94.1% to 95.3%

1. Newer anticoagulant drugs do not require monitoring and produce different outcomes when used for different clinical indications. In which of the following circumstances would you be most likely to prescribe a newer anticoagulant?

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This is a bigger benefit. A reduction in mortality from 5% to 3% is a 40% RRR: 2/5=40%

Perspective
FEBRUARY 22, 2018

The Psychology of Clinical Decision Making — Implications for Medication Use

Jerry Avorn, M.D.

NEJM, February 22nd 2018

"We are moved by the prospect of harms or losses more than by identically sized benefits or gains."

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SPECIAL ARTICLES

ON THE ELICITATION OF PREFERENCES FOR ALTERNATIVE THERAPIES

BARBARA J. MCNEIL, M.D., PH.D., STEPHEN G. PAUKER, M.D., HAROLD C. SOX, JR., M.D., AND AMOS TVERSKY, PH.D.

Abstract We investigated how variations in the way information is presented to patients influence their choices between alternative therapies. Data were presented summarizing the results of surgery and radiation therapy for lung cancer to 238 ambulatory patients with different chronic medical conditions and to 491 graduate students and 424 physicians. We asked the subjects to imagine that they had lung cancer and to choose between the two therapies on the basis of both cumulative probabilities and life-expectancy data. Different groups of respondents received input data that differed only in whether or not the treatments were identified and whether the outcomes were framed in terms of the probability of living or the probability of dying.

In all three populations, the attractiveness of surgery, relative to radiation therapy, was substantially greater when the treatments were identified rather than unidentified, when the information consisted of life expectancy rather than cumulative probability, and when the problem was framed in terms of the probability of living rather than in terms of the probability of dying.

We suggest that an awareness of these effects among physicians and patients could help reduce bias and improve the quality of medical decision making. (N Engl J Med. 1982; 306:1259-62.)

NEJM 1982;306:1259-62

The anticoagulant data from the patient perspective:

Imagine if a patient had been asked to take a drug because it reduced the odds of a major clinical event by 20%.

But then they read on a health blog that the benefit of a years worth of therapy was that their likelihood of not having a major clinical event rose from about 95% to about 96%.

Any of us might feel a little mislead….

2. New GOLD guidelines for COPD have reduced the role of inhaled steroids in favor of dual, long-acting bronchodilator therapy (LAMA+LABA). Compared to single long-acting bronchodilator therapy, which of the following accurately reflects the cost effectiveness of dual bronchodilator therapy?

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Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study

Jadwiga A Wedzicha, Marc Decramer, Joachim H Ficker, Dennis E Niewoehner, Thomas Sandström, Angel Fowler Taylor, Peter D'Andrea, Christie Arrasate, Hungta Chen, Donald Banerji

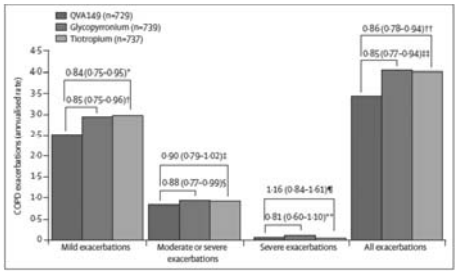
Lancet, May 2013: Dual bronchodilator vs. monotherapy

COPD exacerbations in clinical trials represent an opportunity to be creative with endpoints and they are common (unlike MI or death). The SPARK trial:

Findings Between April 27, 2010, and July 11, 2012, 741 patients were randomly assigned to receive QVA149, 741 to receive glycopyrronium, and 742 to receive tiotropium (729, 739, and 737 patients, respectively, analysed for efficacy). QVA149 significantly reduced the rate of moderate to severe exacerbations versus glycopyrronium by 12% (annualised rate of exacerbations 0·84 [95% CI 0·75–0·94] vs 0·95 [0·85–1·06]; rate ratio 0·88, 95% CI 0·77–0·99, p=0·038). Adverse events (including exacerbations) were reported for 678 (93%) of 729 patients on QVA149, 694 (94%) of 740 on glycopyrronium, and 686 (93%) of 737 on tiotropium. Incidence of serious adverse events was similar between groups (167 [23%] patients

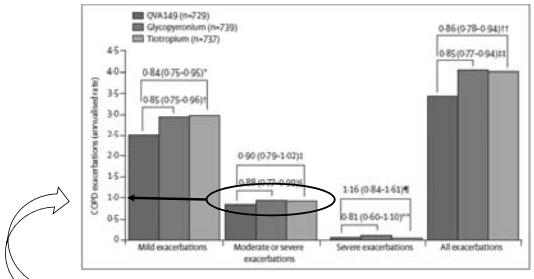
Rather than ~ 95% of patients NOT having primary events (like MI or stroke in CV trials), we now have ~ 95% HAVING primary events…

This makes sense. Our sick COPD patients have a lot of exacerbations. But what are we talking about – need for an antibiotic, hospitalization??



SPARK trial, May 2013

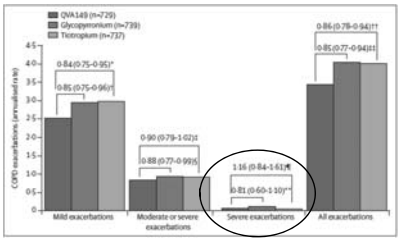
Mild exacerbation: managed at home, usually with a little more acute reliever (i.e. albuterol)
Moderate: requiring antibiotic or steroid (so accessing and utilizing health care resources)
Severe: resulting in hospitalization



SPARK trial, May 2013

And the y-axis here is rate per patient per year

So, how many patients do I need to treat and what does it cost to use dual bronchodilator therapy to avoid one moderate or severe exacerbation?



A: For severe (requiring hospitalization) the cost is infinity

How effective is it to use LAMA + LABA to avoid a moderate exacerbation (requiring an oral steroid or antibiotic)?

Per every 100 patients treated, about 94 have a moderate exacerbation on monotherapy vs. 84 on dual bronchodilator:

Moderate or severe exacerbations (2610 events)			
QVA149 (n=729)	812	1·11 (1·35)	0·84 (0·75–0·94)
Glycopyrronium (n=739)	900	1·22 (1·48)	0·95 (0·85–1·06)
Tiotropium (n=737)	898	1·22 (1·66)	0·93 (0·83–1·04)

So, if I treat 100 patients with dual bronchodilator for one year, 10 will avoid a moderate exacerbation. The "number needed to treat" for one patient to avoid a moderate exacerbation is therefore 10 (100/10)

Therefore..

AWP per inhaler is ~ $400 per month x 12 months of therapy x 10 patients needed to treat = $48,000 to avoid one exacerbation requiring a steroid or antibiotic

2. New GOLD guidelines for COPD have reduced the role of inhaled steroids in favor of dual, long-acting bronchodilator therapy (LAMA+LABA). Compared to single long-acting bronchodilator therapy, which of the following accurately reflects the cost effectiveness of dual bronchodilator therapy?

   a. Compared to a single long-acting bronchodilator, dual therapy reduces a COPD hospitalization at a cost of about $100,000 per hospitalization avoided
   b. Compared to a single long-acting bronchodilator, dual therapy reduces a COPD exacerbation requiring a systemic steroid or antibiotic at a cost of about $50,000 per exacerbation avoided

That's crazy right?
"Mrs. Jones, I'm going to charge you $48,000 for additional inhaled therapy to avoid the need to use an antibiotic or oral steroid burst for a moderate COPD exacerbation."

And yet….knowing this is unlikely to change our decision the next time we face a COPD patient with ongoing symptoms of COPD on a single long-acting bronchodilator

Perspective
FEBRUARY 22, 2018

The Psychology of Clinical Decision Making — Implications for Medication Use

Jerry Avorn, M.D.

"The bias of the individual patient…."

NEJM; April 19, 1990

OCCASIONAL NOTES

DISCREPANCY BETWEEN MEDICAL DECISIONS FOR INDIVIDUAL PATIENTS AND FOR GROUPS

Stanford University
Stanford, CA 94305

DONALD A. REDELMEIER, M.D.
AMOS TVERSKY, PH.D.

Our results are consistent with the notion that physicians give more weight to the personal concerns of patients when considering them as individuals and more weight to general criteria of effectiveness when considering them as a group. For example, the re-

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College of Pharmacy

So, resource utilization for the health of our individual patient does not always align well with the health of the health care system and Big PHARMA is pretty good at exploiting that so it is good to be aware of our biases

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Oregon State
UNIVERSITY
College of Pharmacy

Summary:

1. Drugs are developed to treat disease and are often very inefficient at preventing disease (higher NNT)
2. Expensive drugs used in inefficient settings (dual bronchodilator) add significant cost burden to the health system
3. Being aware of our human biases may help us use drugs better

Thank you

Atrial Fibrillation: When is ablation helpful?

Babak Nazer, MD
Assistant Professor of Medicine and Biomedical Engineering
Knight Cardiovascular Institute
Oregon Health and Sciences University

nazer@ohsu.edu

Disclosures

- St. Jude Medical - investigator-initiated research grant
- Biosense-Webster – investigator-initiated research grant

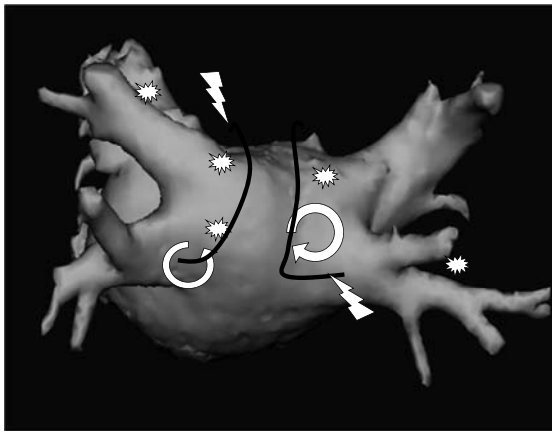
Syllabus:
When is ablation helpful?

1. After risk factor modification
2. Not too early, not too late
3. The Young and the Breathless
    1. Symptomatic AF
    2. Young
    3. CHF
4. Antiarrhythmic drug-resistant

AF Ablation: patient experience

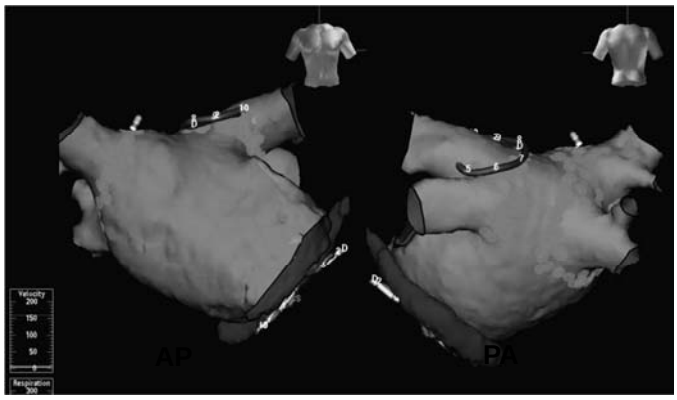
1. Outpatient procedure with overnight stay
2. General anesthesia, radial arterial line +/- Foley, IV heparin
3. R or bilateral femoral venous access
4. One week recovery
    -no exercise
    -mild pleuritic chest pain
    -mild groin discomfort

AF: Pulmonary vein triggers



"Pulmonary Vein Isolation"

“Pulmonary Vein Isolation”



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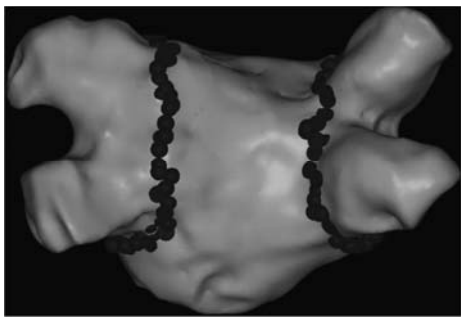
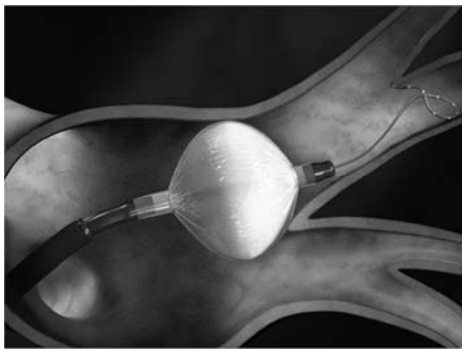


CryoBalloon



Complications of AF Ablation

Updated Worldwide Survey on the Methods, Efficacy, and Safety of Catheter Ablation for Human Atrial Fibrillation

Riccardo Cappato, Hugh Calkins, Shih-Ann Chen, Wyn Davies, Yoshito Iesaka, Jonathan Kalman, You-Ho Kim, George Klein, Andrea Natale, Douglas Packer, Allan Skanes, Federico Ambrogi and Elia Biganzoli

Table 7. Major Complications in the Overall Population

Type of Complication	No. of Patients	Rate, %
Death	25	0.15
Tamponade	213	1.31
Pneumothorax	15	0.09
Hemothorax	4	0.02
Sepsis, abscesses, or endocarditis	2	0.01
Permanent diaphragmatic paralysis	28	0.17
Total femoral pseudoaneurysm	152	0.93
Total artero-venous fistulae	88	0.54
Valve damage/requiring surgery	11/7	0.07
Atrium-esophageal fistulae	6	0.04
Stroke	37	0.23
Transient ischemic attack	115	0.71
PV stenoses requiring intervention	48	0.29
Total	741	4.54

- **20,825 procedures**
- **16,309 patients**

Cappato et al. Circulation EP 2010;3:32-38.

When is ablation helpful?

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   1. Symptomatic AF
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   3. CHF
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Atrial Fibrillation Treatment 3 pillars

1. **Rate Control**
2. **Rhythm Control**
3. **Anticoagulation**

Atrial Fibrillation Treatment 4 pillars

1. **Risk Factor Modification**
2. **Rate Control**
3. **Rhythm Control**
4. **Anticoagulation**

Atrial Fibrillation Treatment: 4 pillars

1. Risk Factor Modification

-Obstructive sleep apnea

-STOP-BANG score[1]

-refer for sleep study

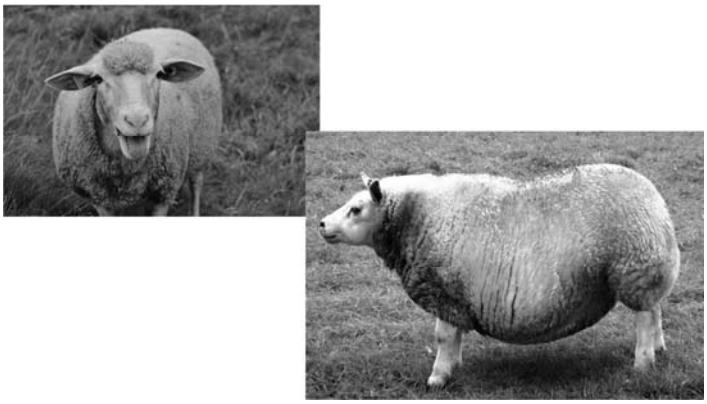
-Alcohol use

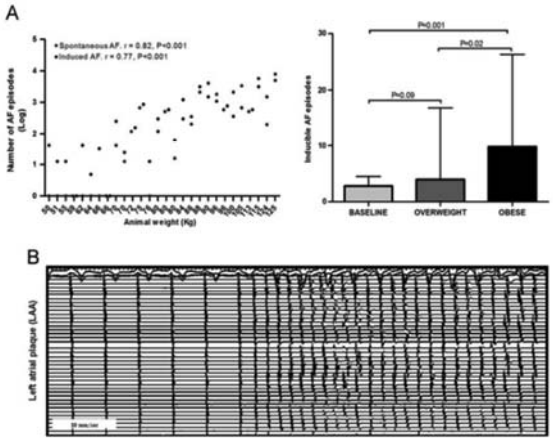
-increased risk for AF > 7 drinks/week[2]

-Obesity

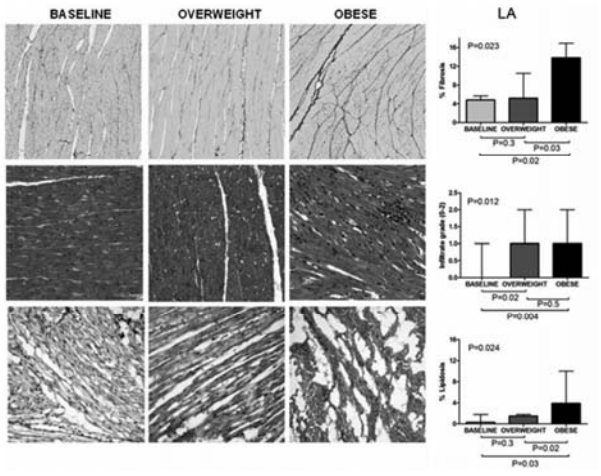
-Hyperthyroidism (rare)

1. Nagappa M, et al. PLoS One 2015.
2. Larsson SC, et al. JACC 2014.





Abed et al. Heart Rhythm 2012.



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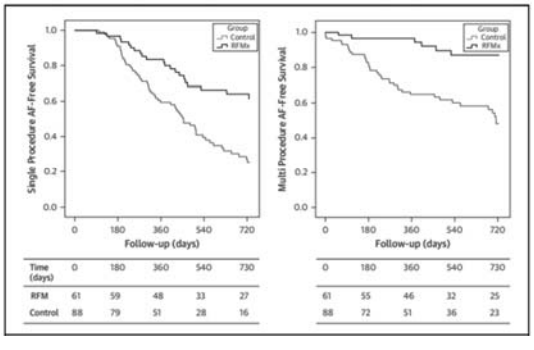
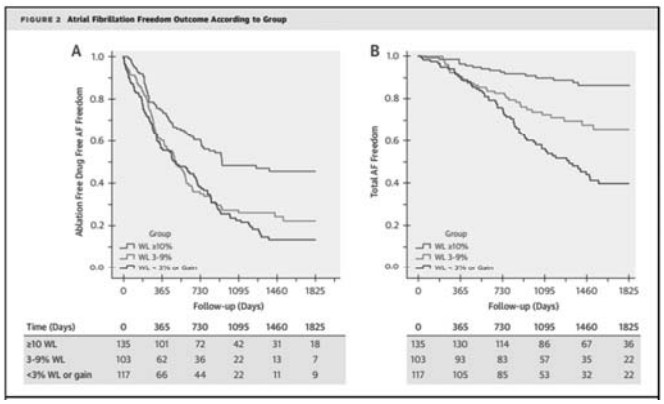


ARREST-AF. Pathak R et al. JACC 2014.



LEGACY-AF. Pathak R et al. JACC 2015.

Atrial Fibrillation Treatment: 4 pillars

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-Obstructive sleep apnea

-STOP-BANG score[1]

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Natural History of AF

Paroxysmal → Persistent → Long-standing persistent

Natural History of AF

Paroxysmal → Persistent → Long-standing persistent

Ablation success (off drug): **70-80%** **50-60%** **30-40%**

EP's enthusiasm:



Outline:
When is ablation helpful?

1. After risk factor modification
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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

CASTLE-AF. Marrouche NF, et al. NEJM 2018

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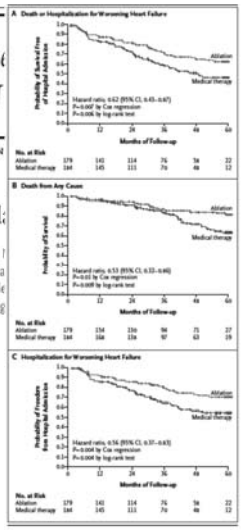

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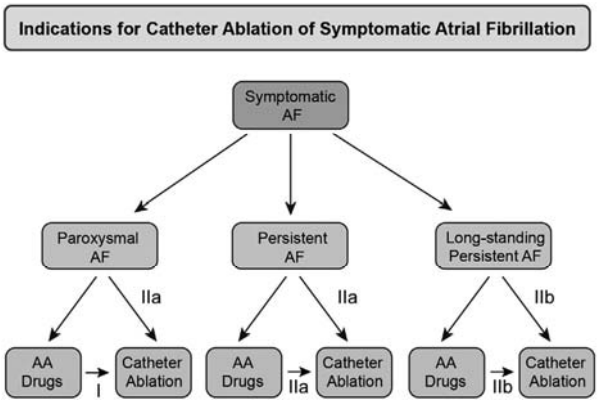
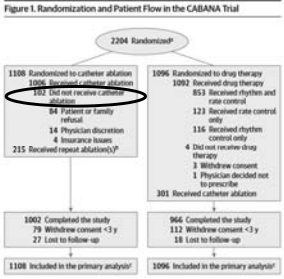


2017 Expert Consensus Statement on Catheter and Surgical Ablation of AF. Heart Rhythm 2017

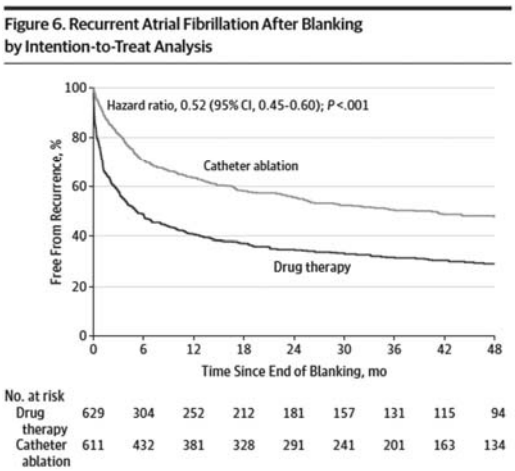
JAMA | Original Investigation

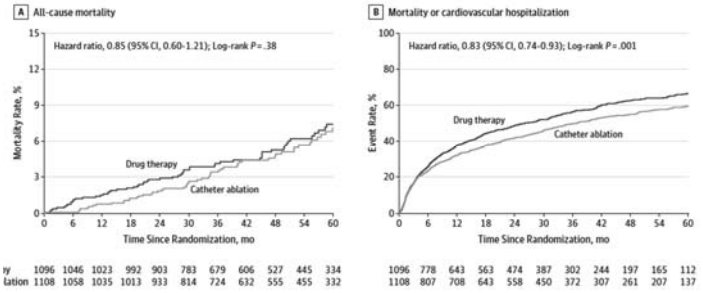
Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation
The CABANA Randomized Clinical Trial

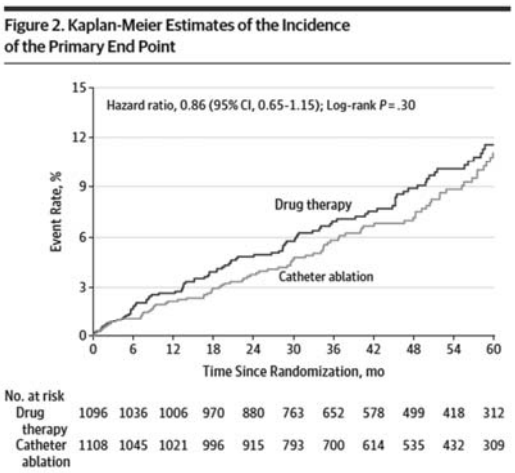
Douglas L. Packer, MD; Daniel B. Mark, MD, MPH; Richard A. Robb, PhD; Kristi H. Monahan, RN; Tristram D. Bahnson, MD; Jeanne E. Poole, MD; Peter A. Noseworthy, MD; Yves D. Rosenberg, MD, MPH; Neal Jeffries, PhD; L. Brent Mitchell, MD; Greg C. Flaker, MD; Evgeny Pokushalov, MD; Alexander Romanov, MD; T. Jared Bunch, MD; Georg Noelker, MD; Andrey Ardashev, MD; Amiran Revishvili, MD; David J. Wilber, MD; Riccardo Cappato, MD; Karl-Heinz Kuck, MD; Gerhard Hindricks, MD; D. Wyn Davies, MD; Peter R. Kowey, MD; Gerald V. Naccarelli, MD; James A. Reiffel, MD; Jonathan P. Piccini, MD, MHS; Adam P. Silverstein, MS; Hussein R. Al-Khalidi, PhD; Kerry L. Lee, PhD; for the CABANA Investigators



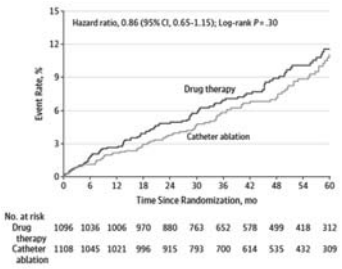
Packer DL, et al. JAMA 2019



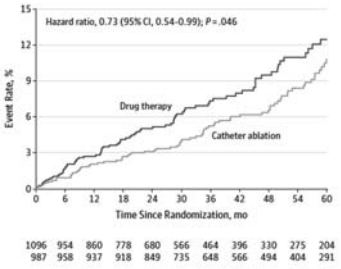




Intention to treat

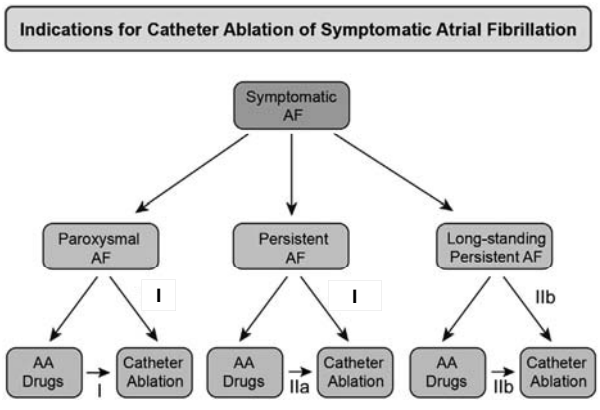


Per-protocol



Jared Miller's Interpretation of CABANA Interpretations

- If you write editorials about how rhythm control is overrated, procedures aren't scrutinized enough before being approved/performed, medical spending is out of hand
  - It's settled! We shouldn't be doing AF ablation
- If you ablate AF for a living and just don't want to hear it
  - It's settled! Everyone should get an AF ablation
- If you're being reasonable
  - It's complicated



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   1. Symptomatic
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4. Antiarrhythmic drug-resistant

Updates in Allergy

Internal Medicine Review – April 12th, 2019

Shyam Joshi, MD
Assistant Professor of Medicine
Section of Allergy and Immunology

Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

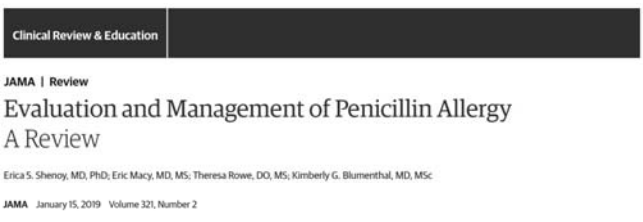
Objectives

- Characterize and stratify penicillin allergic reactions
- Determine which patients should undergo penicillin allergy evaluations
- Identify new areas of food allergy research and treatment options
- Compare treatment options for allergic rhinitis

Presentation Outline

- Penicillin Allergy
  - Shenoy ES, et al. *JAMA*, 2019.
- Food Allergies
  - Sampson HA, et al. *JAMA*, 2017.
  - Bird, et al. *J Allergy Clin Immunol Pract*, 2018.
- Allergic Rhinitis
  - Dykewicz MS, et al. *Ann Allergy Asthma Immunol*, 2017.

Penicillin Allergy


Clinical Review & Education

JAMA | Review

Evaluation and Management of Penicillin Allergy
A Review

Erica S. Shenoy, MD, PhD; Eric Macy, MD, MS; Theresa Rowe, DO, MS; Kimberly G. Blumenthal, MD, MSc

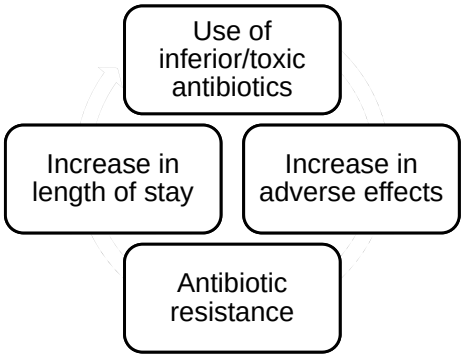
JAMA January 15, 2019 Volume 321, Number 2

Penicillin Allergy

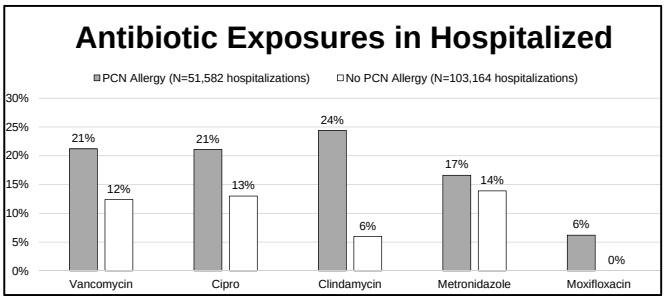
- 8-10% of the US population carries a history of penicillin allergy
  - >95% will tolerate penicillin use after evaluation
- Waning sensitivity to penicillin
  - 50% lose sensitivity by 5 years
  - 80% lose sensitivity by 10 years
- Subsequent penicillin use after negative testing does not increase risk of sensitization

Sogn DD, Evans R, Shepherd GM, et al. *Ann Intern Med*. 1992.
Gadde J, Spence M, Wheeler B, et.al. *JAMA*. 1993.
Macy E, Contreras R. *J Allergy Clin Immunol.* 2014.
Solensky R, Earl HS, Gruchalla, RS. *Arch Intern Med*, 2002.
Dorman SM, Seth S, Khan DA. *J Allergy Clin Immunol Pract*, 2018.

Effects of Penicillin Allergy Label



Antibiotic Exposure



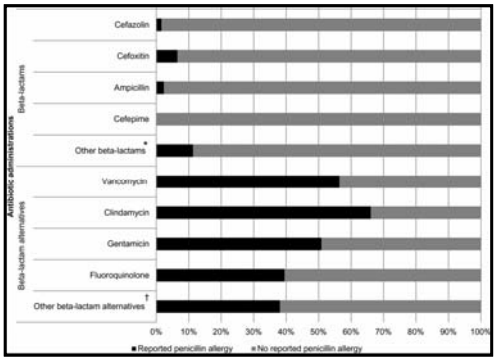
Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.

Outcomes: PCN Allergy Label

1. Higher rate of treatment failures
2. Increased prevalence of Clostridium difficile, MRSA, and VRE
3. Increased future healthcare utilization
4. Increased healthcare dollars
5. Higher rates of surgical site infections

Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.
Jeffres MD, et al. *J Allergy Clin Immunol,* 2016.
Picard M, et al. *J Allergy Clin Immunol Pract,* 2013.
Blumenthal KG, et al. *Clin Infectious Dis*, 2018.

Surgical Site Infections



When controlled for surgery type, age, sex, race, American Society of Anesthesiologists class, procedure duration, and wound class

⇩

51% increased risk of a SSI in patients that have a PCN allergy label (p<0.04)

Blumenthal KG, et al. *Clin Infectious Dis*, 2018.

Choosing Wisely Campaign (2014)

Choosing Wisely
An initiative of the ABIM Foundation

American Academy of Allergy, Asthma & Immunology
American Academy of Allergy Asthma & Immunology

Five Things Physicians and Patients Should Question

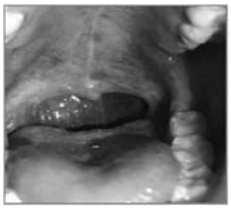
10 Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.

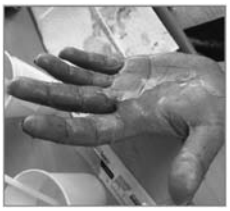
https://www.choosingwisely.org

Severe Cutaneous Adverse Reactions (SCAR)

Severe T-cell-mediated reactions or severe cutaneous adverse reactions

Onset days to weeks into treatment course
Blistering and/or skin desquamation
Mucosal and/or organ involvement
Usually requires hospitalization





Shenoy ES, et al. *JAMA*, 2019.

Stratifying Allergy Risk

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History[a]	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE[b] Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis[b]	Anaphylactic symptoms[c] Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation.[d]	Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e] Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

Low Risk

Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches)
Pruritus without rash
Remote (>10 y) unknown reactions without features of IgE[b]
Family history of penicillin allergy

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Shenoy ES, et al. *JAMA*, 2019.

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Medium Risk

Urticaria or other pruritic rashes
Reactions with features of IgE but not anaphylaxis[b]

Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e]
Consider allergy/immunology referral.

Shenoy ES, et al. *JAMA*, 2019.

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High Risk

Anaphylactic symptoms[c]
Positive skin testing
Recurrent reactions
Reactions to multiple β-lactam antibiotics

Allergy/immunology referral or desensitization.

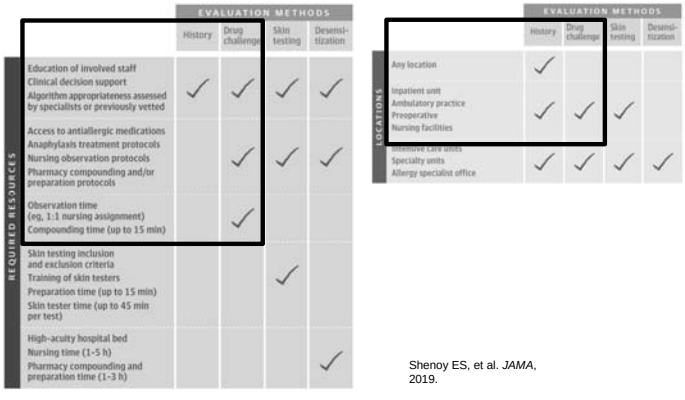
Shenoy ES, et al. *JAMA*, 2019.

Penicillin Testing

- Modified protocol
  - Skin prick and intradermal testing
    - Penicilloyl-polylysine
    - Penicillin G
  - Observed (graded) oral amoxicillin challenge
- NPV of 97-100%
  - PPV not well established

https://www.medscape.com/viewarticle/871833

Whose Responsibility



Shenoy ES, et al. *JAMA*, 2019.

Wallet Card for Patient

ALLERGY INFORMATION

Name: _____

Date of Birth: _____

Allergies:

_____ _____
_____ _____
_____ _____
_____ _____
_____ _____

I am NOT Allergic to Penicillin

Penicillin Skin Testing (Prick and Intradermal) followed by an oral graded Amoxicillin Challenge was performed at Oregon Health and Science University (OHSU) on:

_____.

RESULTS: Negative (No Reaction)

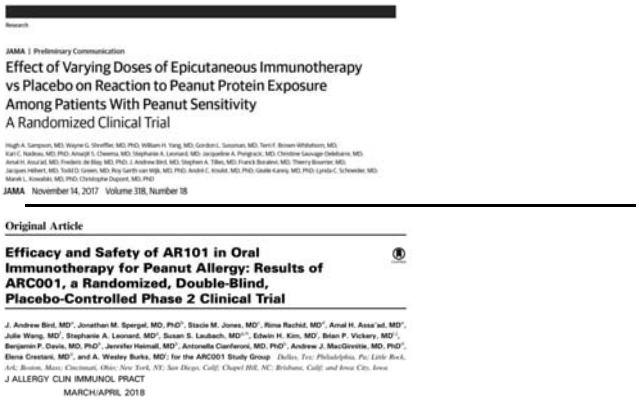
Test performed by _____.

Take Home Points

- 32 million patients have a PCN allergy label
  - >95% of them can actually tolerate penicillin
- Patients with a PCN allergy label have poorer clinical outcomes and higher healthcare costs
- Patients can be risk stratified based on clinical presentation
  - Patients should be evaluated as soon as possible

Shenoy ES, et al. *JAMA*, 2019.

Food Allergies



Research

JAMA | Preliminary Communication

Effect of Varying Doses of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Exposure Among Patients With Peanut Sensitivity
A Randomized Clinical Trial

JAMA November 14, 2017 Volume 318, Number 18

Original Article

Efficacy and Safety of AR101 in Oral Immunotherapy for Peanut Allergy: Results of ARC001, a Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Trial

J ALLERGY CLIN IMMUNOL PRACT
MARCH/APR IL 2018

Food Allergy Epidemiology

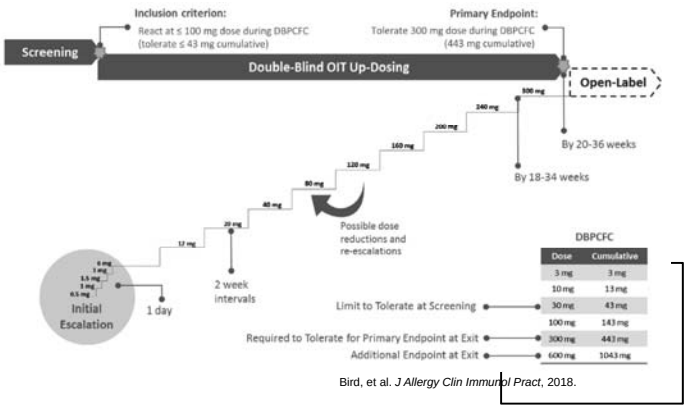
- Potential life threatening condition
  - Affects 5-10% of the US population
- Food Intolerance vs Food Allergy
  - 15-20% of adults report food intolerance
  - Non-immunologic response
- Sensitization vs Clinical Food Allergy
  - 20-40% are sensitized to at least 1 food
  - 5-8% likely have a true food allergy
- 1 in 160 adults have a peanut allergy

Bird, et al. *J Allergy Clin Immunol Pract*, 2018.

Current Treatment Strategies

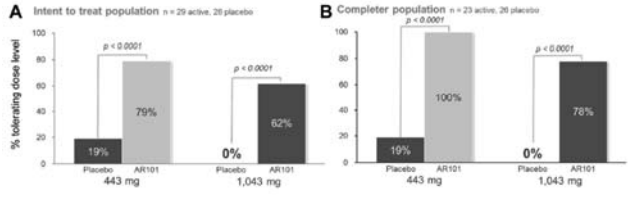
- History/testing/challenge to confirm diagnosis
- Education
- Strict avoidance of culprit food
- Epinephrine autoinjector
  - Antihistamines in certain situations

Oral Peanut Immunotherapy (OIT)



Bird, et al. *J Allergy Clin Immunol Pract*, 2018.

Efficacy of Oral Immunotherapy



Bird, et al. *J Allergy Clin Immunol Pract*, 2018.

Adverse Events of OIT

TABLE E4. Summary of treatment-related treatment-emergent adverse events reported by more than one subject (safety)

MedDRA system organ class/preferred term, n (%)	AR101 (N = 29)	Placebo (N = 26)	Overall (N = 55)
Any event	27 (93%)	12 (46%)	39 (71%)
Immune system disorders	26 (90%)	10 (38%)	36 (65%)
Hypersensitivity	26 (90%)	10 (38%)	36 (65%)
Gastrointestinal disorders	6 (21%)	1 (4%)	7 (13%)
Vomiting	3 (10%)	1 (4%)	4 (7%)
Abdominal pain	2 (7%)	0	2 (4%)
Respiratory, thoracic and mediastinal disorders	3 (10%)	2 (8%)	5 (9%)
Nasal congestion	2 (7%)	1 (4%)	3 (5%)
Oropharyngeal pain	2 (7%)	0	2 (4%)
Skin and subcutaneous tissue disorders	3 (10%)	1 (4%)	4 (7%)
Urticaria	3 (10%)	1 (4%)	4 (7%)

Bird, et al. *J Allergy Clin Immunol Pract*, 2018.

Patch Immunotherapy

All Patients	Placebo-patch (N=49)	50µg-patch (N=51)	100µg-patch (N=47)	250µg-patch (N=49)
Treatment Response at Month 12				
Responders, n (%)[a]	13 (26.5)	24 (47.1)	22 (46.8)	26 (53.1)
95% CI[b]	14.9, 41.1	32.9, 61.5	32.1, 61.9	38.3, 67.5
Eliciting dose ≥1,000 mg after 12 months, n (%)	6 (12.2)	14 (27.5)	17 (36.2)	18 (36.7)
≥10-fold increase in the eliciting dose after 12 months, n (%)	10 (20.4)	16 (31.4)	14 (29.8)	21 (42.9)
Non-responders, n (%)	36 (73.5)	27 (52.9)	25 (53.2)	23 (46.9)
P value vs. placebo[c]	—	—[d]	—[d]	0.01

TEAE Category[a]	Phase 2b Trial (N = 221) Placebo Patch (N = 56)	50-µg Patch (N = 53)	100-µg Patch (N = 56)	250-µg Patch (N = 56)
TEAEs related to investigational product				
Patients, No. (%)	27 (48.2)	51 (96.2)	53 (94.6)	54 (96.4)
Events, No.	82	151	191	215
Any serious TEAE				
Patients, No. (%)	0	2 (3.8)	1 (1.8)	2 (3.6)
Events, No.	0	3	1	2

Sampson HA, et al. *JAMA*, 2017.

Take Home Points

- Differentiation between food allergies and tolerances should always be discussed with patients
  - Common intolerance symptoms include bloating, abdominal discomfort, diarrhea, “brain fog,” headaches, and fatigue
- New therapies for food allergies will be available in the next 1-3 years
  - Oral food immunotherapy
  - Patch food immunotherapy

Allergic Rhinitis

Practice Guideline

Treatment of seasonal allergic rhinitis
An evidence-based focused 2017 guideline update

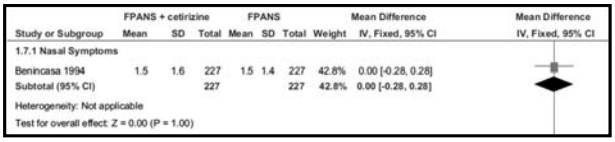
Mark S. Dykewicz, MD; Dana V. Wallace, MD; Fuad Baroody, MD; Jonathan Bernstein, MD; Tim Craig, DO; Ira Finegold, MD; Faith Huang, MD; Desiree Larenas-Linnemann, MD; Eli Meltzer, MD; Gary Steven, MD, PhD; David I. Bernstein, MD; Joann Blessing-Moore, MD; Chitra Dinakar, MD; Matthew Greenhawt, MD, MBA; Caroline C. Horner, MD; David A. Khan, MD; David Lang, MD; John Oppenheimer, MD; Jay M. Portnoy, MD; Christopher R. Randolph, MD; Matthew A. Rank, MD; Workgroup Chair and Cochair: Mark S. Dykewicz, MD; Dana V. Wallace, MD

M.S. Dykewicz et al. / Ann Allergy Asthma Immunol xxx (2017) 1–23

Key Questions

1. Is there benefit of using a combination of an oral antihistamine and an intranasal steroid (INS) compared to monotherapy?
2. How does montelukast compare with an intranasal steroid?
3. Is there clinical benefit using combination therapy with an INS and an intranasal antihistamine compared with monotherapy?

INS +/- Oral Antihistamine

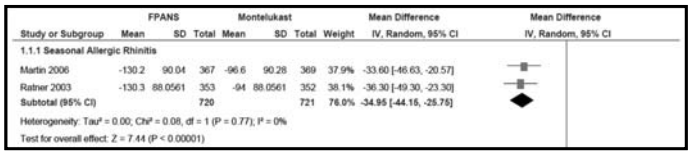


- No change in mini-RQLQ, nasal inspiratory flow, nasal symptom score, nasal NO levels, conjunctivitis score, nasal/eye symptom-free days, headache symptom-free days, rescue medication need, or adverse events.

Summary of analysis
For the treatment of SAR in patients who are 12 years or older, there is no clinical benefit of using a combination of an oral antihistamine and an INCS compared with monotherapy with an INCS.

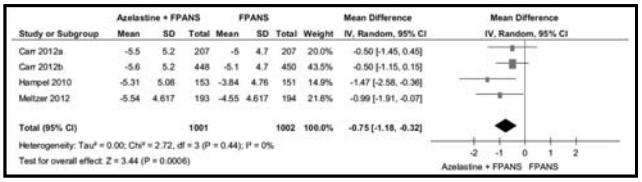
Dykewicz MS, et al. *Ann Allergy Asthma Immunol*, 2017,

Montelukast?



Statistically significant clinical benefit of INS compared with montelukast. Also, addition of montelukast to INS does not produce clinically significant improvements over INS alone.

ICS + Antihistamine Nasal Spray



There was a statistically significant clinical benefit in terms of total nasal symptom reduction when using the combination of an INAH and an INCS but with an increase of adverse events.

Take Home Points

- Initial therapy for allergic rhinitis should be intranasal steroids
- The addition of oral antihistamines to intranasal steroids does not provide any clinically significant benefit
- Intranasal steroids are more effective than monotherapy with montelukast
- The combination of intranasal steroids and intranasal antihistamines is more effective than either as monotherapy

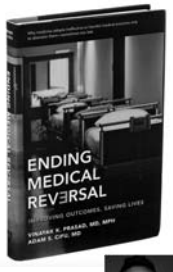
Questions?

OHSU
Clinic for
Asthma & Allergic Diseases

OHSU
Combined Clinic for Severe Sinus Disease
ENT & Allergy

High Value Care

Disclosure



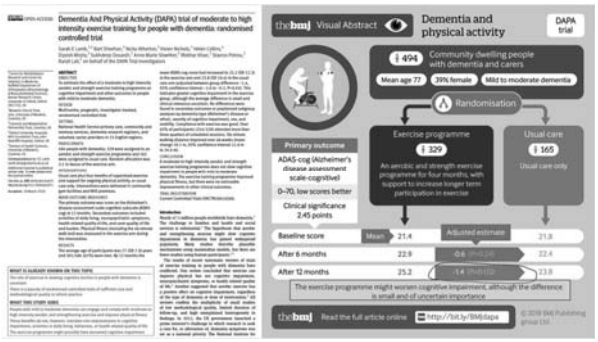
Funding:

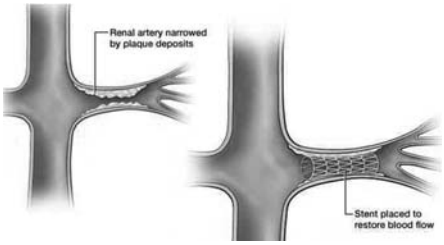
ljaf
laura and john arnold foundation

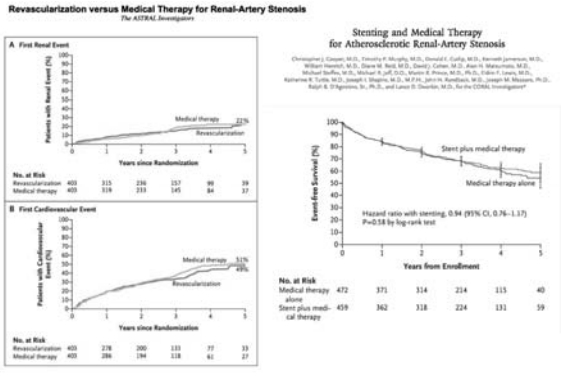
Twitter @VPrasadMDMPH

- High value therapies
- High value diagnosis

Another reminder why we need MORE not LESS RCTs.



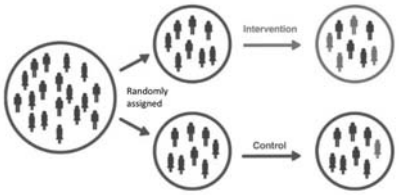


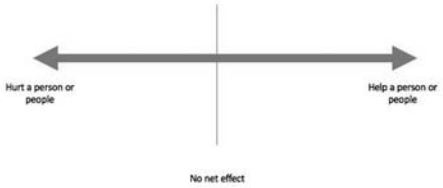


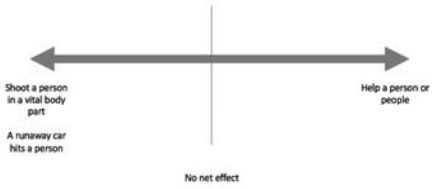
- High value therapies
  - Absence of evidence is not evidence of absence
  - You can't have an RCT for everything
  - Parachutes

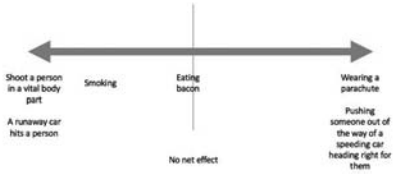
RCT Misconceptions

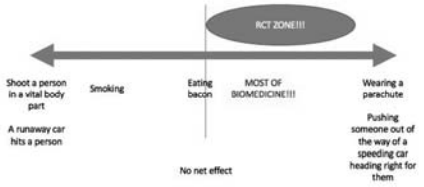
When SHOULD we do randomized trials in biomedicine and beyond, and when SHOULD we not do them/ don't need to do them?











Because those are interventions where human beings' bias, optimism, and profiteering may result in an incorrect assessment of the effect, and only carefully done RCTs can CLARIFY if + or - and if worth it

What about an RCT of smoking?

- That makes no sense b/c we don't do RCTs of putative harms. We also don't have an RCT of a gun shot wound being harmful or drinking a glass of benzene.

With some voluntary/ desired exposures, you can flip the question.

- We could actually do an RCT of smoking cessation counseling efforts in some high risk groups. You can find the place where you postulate a modest benefit and test it. And SHOULD.

We don't do RCTs to find rare adverse events.

- Correct, we do not. RCTs do not answer all questions. They don't tell you your kid's birthday. They DO test if modest to marginal effect putative benefit interventions are real or bullshit.

What about RCTs of parachutes?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score >15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

What about RCTs of parachutes?

- Two limits of the analogy
  1. A single clear etiology (BCR-ABL)
     Trauma –
  2. A huge effect size

Prior "parachutes" were no such thing

RESEARCH

Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials

OPEN ACCESS

Results Four randomised controlled trials with a total of 900 patients (470 antibiotic treatment, 430 appendicectomy) met the inclusion criteria. Antibiotic treatment was associated with a 63% (277/436) success rate at one year. Meta-analysis of complications showed a relative risk reduction of 31% for antibiotic treatment compared with appendicectomy (risk ratio (Mantel-Haenszel, fixed) 0.69 (95% confidence interval 0.54 to 0.89); I^2=0%; P=0.004). A secondary analysis, excluding the study with crossover of patients between the two interventions after randomisation, showed a significant relative risk reduction of 39% for antibiotic therapy (risk ratio 0.61 (0.40 to 0.92); I^2=0%; P=0.02). Of the 65 (20%) patients who had appendicectomy after readmission, nine had perforated appendicitis and four had gangrenous appendicitis. No significant differences were seen for treatment efficacy, length of stay, or risk of developing complicated appendicitis.

Conclusion Antibiotics are both effective and safe as primary treatment for patients with uncomplicated acute appendicitis. Initial antibiotic treatment merits consideration as a primary treatment option for early uncomplicated appendicitis.

Most medical practices don't have large treatment effects

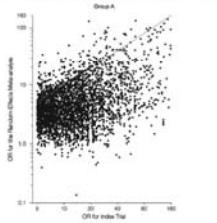
ORIGINAL CONTRIBUTION

Empirical Evaluation of Very Large Treatment Effects of Medical Interventions

Tiago V. Pereira, PhD
Ralph I. Horwitz, MD
John P. A. Ioannidis, MD, DSc

Context Most medical interventions have modest effects, but occasionally some cli
ed trials may find very large effects for benefits or harms.
Objective To evaluate the frequency and features of very large effects in medic

Figure 2. Treatment Effects in Index Trials vs the Meta-analysis of All Trials



Some advances have been tested without RCT

When are randomised trials unnecessary? Picking signal from noise

The relation between a treatment and its effect is sometimes so dramatic that bias can be ruled out as an explanation. **Paul Glasziou and colleagues** suggest how to determine when observations speak for themselves

Some historical examples of treatments with dramatic effects

- Insulin for diabetes[41]
- Blood transfusion for severe haemorrhagic shock[42]
- Sulphanilimide for puerperal sepsis[43]
- Streptomycin for tuberculous meningitis[44]
- Defibrillation for ventricular fibrillation[45]
- Closed reduction and splinting for fracture of long bones with displacement
- Salicin for acute rheumatism[46]
- Neostigmine for myasthenia gravis[47]
- Tracheostomy for tracheal obstruction[48]
- Suturing for repairing large wounds
- Drainage for pain associated with abscesses
- Pressure or suturing for arresting haemorrhage
- Ether for anaesthesia
- One way valve or underwater seal drainage for pneumothorax and haemothorax[49]
- Phototherapy for skin tuberculosis[50]
- Combination chemotherapy with cisplatin, vinblastine, and bleomycin for disseminated testicular cancer

cmajOPEN

Most medical practices are not parachutes: a citation analysis of practices felt by biomedical authors to be analogous to parachutes

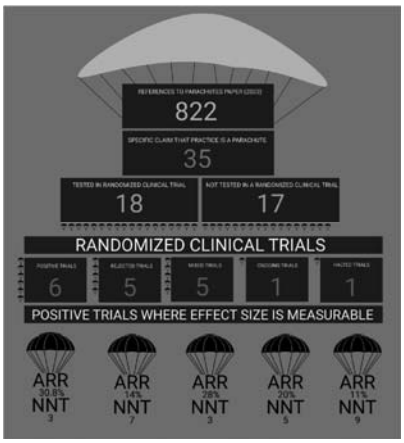
Michael J. Hayes, MD, Victoria Kaestner, BA, Sham Mallarkody, MBBS, Vinay Prasad, MD, MPH

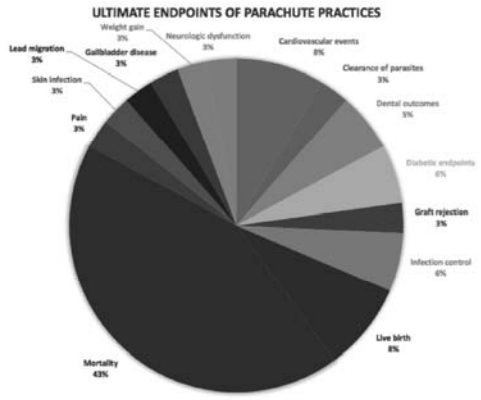
Author Affiliations

Correspondence to:
Vinay Prasad, prasad@ohsu.edu

Abstract

Background: In a 2003 paper in BMJ, the authors made the tongue-in-cheek observation that there are no randomized controlled trials (RCTs) of parachutes. This paper has been widely read, cited and used to argue that RCTs are impractical or unnecessary for some medical practices. We performed a study to identify and evaluate claims that a medical practice is akin to a parachute.





The sobering fact is that most of what we do has modest or marginal effects (if they work at all).

Don't be embarrassed! Celebrate it!

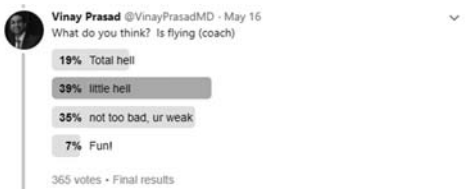
2018 marks a rare period in human history where some of our interventions actually make a modest impact!

Proof:

Can non-randomized, observational studies work just as well as RCTs here? I truly do not know. We have a paper under review that we try to help provide ways to make them better. It will take a lot of time and research and CONCORDANCE studies to know

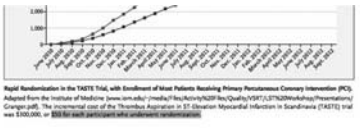
Now I am going to add my thoughts on RCT cost being prohibitive or otherwise bureaucratic or cumbersome. First, lets separate randomization from the man made problems of RCTs Just like we separate the Boeing aircraft from united airlines.

There is nothing wrong with the Boeing 787 or even 737. They are fine planes. Very good even. Yet, commercial flying is a hellish experience.



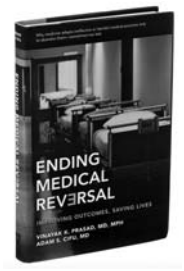
- Yet, the airlines have made flying miserable. But no one blames the plane. Similarly, we have made RCTs impractical or costly or painful, but we can't blame the RCT for that. We have to blame ourselves.

In one European RCT called TASTE, the authors conducted it for $50 per participant



What is High Value Diagnosis?

& other questions



@VPrasadMDMPH

PROBLEMATIC PAIN…

MAKING THE INTERVIEW COUNT FOR PATIENT AND CLINICIAN

Steve Wahls, MD, FAAFP
OHSU Department of Family Medicine
&
Chloe Ackerman, PsyD
Ackerman Psychological Services
Scappoose, OR

OHSU 28th Annual Internal Medicine Review, April 12, 2019

Disclosures

Neither of us have financial associations to disclose.

Skit "A Patient In Pain"

What did you feel?

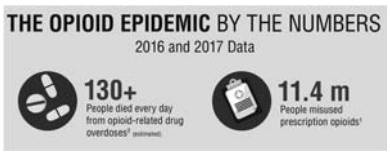
Learning Objectives:

- Define chronic pain.
- Describe examples of emotional interference and resilience impacting pain perception and experience.
- Apply knowledge of resilience factors to patient and provider in pain management.
- Interview a patient with chronic pain and achieve empathy, increase patient buy-in, and redirect conflict.

Scope of the problem:

"Most recently, analysis of data from the 2012 National Health Interview Study showed that 11.2% of adults report having daily pain. On the basis of data available from health systems, researchers estimate that 9.6–11.5 million adults, or approximately 3%–4% of the adult U.S. population, were prescribed long-term opioid therapy in 2005."

Office of Clinical Integration and EBP, 2017 OHSU Health System, August 2017



Reducing the Opiate Risk: CDC

CLINICAL REMINDERS

- Opioids are not first-line or routine therapy for chronic pain
- Establish and measure goals for pain and function
- Discuss benefits and risks and availability of nonopioid therapies with patient

CDC U.S. Department of Health and Human Services Centers for Disease Control and Prevention

- Evaluate risk factors for opioid-related harms
- Check PDMP for high dosages and prescriptions from other providers
- Use urine drug testing to identify prescribed substances and undisclosed use
- Avoid concurrent benzodiazepine and opioid prescribing
- Arrange treatment for opioid use disorder if needed

https://www.cdc.gov/drugoverdose/pdf/Guidelines_Factsheet-a.pdf

Then there's pushback…

THE LUND REPORT
Oregon's most vital source of health news

Oregon Backs Off Opioid Cutoff Plan For Chronic Pain Patients, Adding Non-drug Treatments

Guidelines discussed Wednesday would align recommendations for opioid prescribing for back pain and five other chronic pain conditions, adding new treatments like yoga, behavioral therapy and massage.

By: Lynne Terry

Dec 5 2018

Our pinch as providers…

OPG
OREGON PAIN GUIDANCE

The problem we now face is the "legacy patients," those who have been on high-dose daily opioids for years, sometimes passing from provider to provider. Many primary care practitioners care for these patients, though they may not have initiated the opioid treatment regimen. These individuals deserve compassionate care and may sincerely believe that they could not cope without continuing their medication regimen. However, current best practice suggests that a slow-dosage reduction will improve the quality of life for the majority of patients.

https://www.oregonpainguidance.org/guideline/treating-chronic-pain/ accessed 2019-03-19

Filling the Opiate Gap:

- Treatment of chronic pain is changing in Oregon and beyond.
- Insurers including Oregon Health Plan are broadening coverage:
  - Acupuncture
  - Massage
  - Chiropractic services
  - Integrative Pain clinics

Oregon Health Authority Oregon Pain Management Commission

Pain Care Toolbox

Filling the Opiate Gap: Opportunity

- We have an opportunity to change how we think about caring for patients with chronic pain.
  - Better questions
  - Better understanding between patients and providers
  - Better teaching

The Pain Problem…

What is chronic pain?

Definition: any pain lasting more than 12 weeks

- Triggers:
  - Injury
  - Ongoing cause, such as illness
  - No clear cause
- Associations:
  - Fatigue
  - Sleep disturbance
  - Decreased appetite, and mood changes
  - Reduced movement, which can reduce flexibility, strength, and stamina. Difficulty in carrying out important and enjoyable activities can lead to disability and despair.

(NIH Medline Plus, 2011)

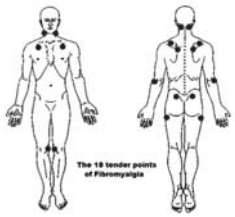
Chronic Pain Prevalence:

Defined as "Chronic, recurrent, or long-lasting pain lasting for at least 6 months"…

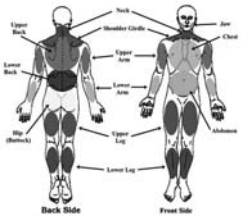
- Chronic pain prevalence 30.7%.
- Females > males; increased with age
- 50% with chronic pain experienced daily pain
- Average (past 3 months) pain intensity was "severe" for 32%
- Socioeconomic correlates: low household income and unemployment

(Johannes, Le, Zhou, Johnston, & Dworkin, 2010)

Chronic Pain Prototype:



1990



2010

ACR: Fibromyalgia Syndrome

(Wolfe et al, 2010)

Causes/Risk Factors

- Fibromyalgia Associations (weak) with disease onset:
  - Stressful or traumatic events: MVAs, post-traumatic stress disorder (PTSD)
  - Repetitive injuries
  - Illness (e.g., viral infections)
  - Certain diseases (i.e., lupus, rheumatoid arthritis, chronic fatigue syndrome)
  - Obesity
- Abnormal pain processing: React more strongly
- Associations with depression and anxiety

(CDC, 2015)

Tender Points & Stress:

- Loss of parents
- More somatic symptoms
- Low levels of self care
- Increased fatigue
- Pattern of illness behavior/ increased medical care
- **Abuse** *

OR 2.1

OR 6.6

(Mcbeth, Macfarlane, Benjamin, Morris, & Silman, 1999)

Adverse Childhood Experiences:

Prevalence

Self-reported childhood individual ACEs:

- Abuse
  - Emotional abuse 10.6%
  - Physical abuse 28.3%
  - Sexual abuse 20.7%
- Neglect
  - Emotional neglect 14.8%
  - Physical neglect 9.9%
- Household dysfunction
  - Mother treated violently 12.7%
  - Household substance abuse 19.4%
  - Household mental illness 19.4%
  - Parental Separation 23.3%
  - Incarcerated household member 4.7%

(Casanova, 2012)

Adverse Childhood Experiences:

Increased number, increased risk for:

- Alcoholism and alcohol abuse
- Chronic obstructive pulmonary disease
- Depression
- Fetal death
- Health-related quality of life
- Illicit drug use
- Ischemic heart disease
- Liver disease
- Poor work performance
- Financial stress
- Risk for intimate partner violence
- Multiple sexual partners
- Sexually transmitted diseases
- Smoking
- Suicide attempts
- Unintended pregnancies
- Early initiation of smoking
- Early initiation of sexual activity
- Adolescent pregnancy
- Risk for sexual violence
- Poor academic achievement

(Casanova, 2012)

Interpersonal trauma and somatic symptoms

- 597 urban primary care <u>patients with chronic pain</u> surveyed about:
  - sexual trauma (ST)
  - intimate partner violence (IPV)
  - childhood trauma history (3 + ACE)
- Mediators: PTSD, Depression, Substance abuse
- Dependent: somatic symptom severity
- Women: depression… more severe symptoms
- Men: depression & substance abuse.

(McCall-Hosenfeld, Winter, Heeren, & Liebschultz, 2014)

How does chronic pain affect our patients?

- Increased medical bills
- Decreased income
- Lower living standards
- Difficulty with ADL's
- Decreased ability to engage in enjoyable activities
- Role change
- Emotional distress
- Depression
- Mental exhaustion
- Anxiety
- Fatigue
- Catastrophizing

And then the health care provider…

(That's us!)

Provider Burnout…

- More than half of US physicians report *<u>burnout.</u>*
- Primary care providers report the highest rates of burnout.
- Measures of burnout:
  - Lack of sense of personal accomplishment
  - Emotional exhaustion
  - Depersonalization

Kroll, Macauley, & Jesse, 2016

Challenges in caring for those with chronic pain:

- Diagnostic uncertainty
- Lack of clear research guiding treatment choices
- Inadequate time, resources, and training in pain management
- Costly interventions with limited efficacy
- Lack of trust in patient-provider relationship
- Emotional toll on providers

Kroll, Macauley, & Jesse, 2016

Resilience

The personal qualities and skills that allow for an individual's healthy/successful functioning or adaptation within the context of significant adversity or a disruptive life event.

(Lee et al., 2013)
Picture Credit: Go Your Own Road, Erik Johansson

Pain Resilience

- Positive self-talk
- Social support
- Sense of control
- Task persistence

- Lack of:
  - Guarding
  - Emotional interference
  - Catastrophizing
  - Disability beliefs
  - Belief in a medical cure
  - Pain-induced fear

(Karoly & Ruehlman, 2006; West, Foster, & Usher, 2012)

Skit: A Patient in Pain (Reprise)

What did you feel?

"THE INTERVIEW IS THE INTERVENTION"

Think outside the pill bottle!

Interview Strategies

1. Relationship: "I am here because I care for your wellbeing."
2. Empathy: "This feels hard and scary."
3. Resilience: "You already have tools to work with."
4. Education: "Our medical knowledge changes."
5. Planning: "I will not leave you alone without an alternative plan."
6. Most importantly: "I hear you."

The Interview: Relationship

- Questions
  - Can you tell me when you're starting to feel anxious or frustrated as we talk about this?
  - I get the sense that you're starting to feel pretty frustrated with me. Can you tell me about that?
- Reflections
  - I wonder if you came into this appointment today feeling like you were going to have to argue with me to get what you need
  - I feel like we're getting into a power struggle, and I want to make sure we stay on the same page. You want help, and I want to help you

The Interview: Empathy

- Questions
  - Tell me about how this medication has helped you in the past
  - What are you afraid will happen when *(not if!)* we taper your medication?
- Reflections
  - I wonder if it feels like you have to prove to me that your pain is bad enough to need the medication
  - You probably feel like losing these meds means losing the last thing keeping the pain at bay

The Interview: Identifying Resilience

- Resilience-based questions
  - **Task persistence:** How do you talk yourself through a pain episode?
  - **Catastrophic thinking:** What things do you fear most about this pain?
  - **Belief in a medical cure:** What do you hope I will do for your pain? What are your pain treatment goals?
  - **Pain-induced fear:** Tell me about other times you've felt pain you feared wouldn't go away.
  - **Sense of control**: How have you dealt with pain in the past? Do you notice yourself doing similar things now?

The Interview: Education

- Questions
  - What have you heard from other people or the news about the issues with opioids?
  - Can I tell you some of the new information we have about these medications?
  - What are you thoughts on that information? What was new or surprising to you?

The Interview: Planning

- Questions
  - What activities do you wish you could do?
  - What do you miss about your life before this pain?
  - Tell me about some of the ways you deal with your pain already
- Statements
  - Let's treat this like an experiment. We'll make a plan today, then next time we meet we can see what worked and didn't work. Then with that information, we can make an even better plan next time.

The Interview: Wrapping Up

- Structure: Working within the time frame
  - Short visit: doesn't need to be a therapy session!
  - Set the expectation: "*I have five questions about your history and pain I would like to ask if that's all right.*"
  - Close the discussion: "*Thank you for being so open with me. If you feel like it would be helpful to continue talking to someone about this, we can help you find a therapist/connect you with someone in our clinic who specializes in helping people with similar concerns.*"

Dispensing with Testing in Chronic Pain…

- History and PE are foundational in diagnosis for most chronic pain.
- Don't skimp on your social history!
- No routine lab testing, unless directed by other signs or symptoms…
  - Don't order a test unless you are prepared to explain the answer!

Building Bridges: De-medicalizing our care

- Multimodal approach centered on self management and non-pharmacologic strategies
- Encourage patient to set goals and normalize life
- Graduated exercise program
  - Aerobic more effective
  - Consider supervised exercise
  - Women may benefit from resistance training (reduced fatigue, tenderness, increased well being)
- Psycho-education and formal counseling
- CBT may help reduce fear of pain and activity

How do we get buy in?

- Understand that patient adherence is overall spotty.
- Patient and provider have right to refuse a given approach…
- Healthy provider boundaries are appropriate and necessary.
- Empathy must be established.
- Patient insight is developed in to their problems.
- Patient empowerment to change perspective and behaviors.

Summary

- Chronic pain has significant personal and societal consequences, and contributes to poor patient/provider relationships
- Awareness of patients' emotions around chronic pain can enhance empathy and open doors for additional therapeutic modalities
- A strong interview can build resilience, enhance patient/provider relationship, and serve as an intervention for chronic pain treatment
- Care for chronic pain patients is within the realm of a primary care provider, supported by behavioral health specialists when available

Questions/ Comments?

Thank you for joining us and participating!

SURVIVING CHRONIC PAIN: PUTTING RESILIENCE IN TO PRACTICE

BREAKOUT SESSION

Chloe Ackerman, PsyD
Ackerman Psychological Services
Scappoose, OR
&
Steve Wahls, MD, FAAFP
OHSU Department of Family Medicine

OHSU 28th Annual Internal Medicine Review, April 12, 2019

Disclosures

Neither of us have financial associations to disclose.

Your Experiences…

- What bothers you most when you care for patients who have chronic pain?

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- What bothers you most when you care for patients who have chronic pain?
- What strategies do you use when chronic pain is the main issue?

Your Experiences…

- What bothers you most when you care for patients who have chronic pain?
- What strategies do you use when chronic pain is the main issue?
- Do you have ways to keep your responses in check when faced with a patient who is intensely focused on their pain?

Our Focus…

"THE INTERVIEW IS THE INTERVENTION"

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Skit: A Patient in Pain (Reprise)

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Triad Role **Play**

- ***The key word here is PLAY***
- Don't try to be perfect at this. Make mistakes! It's the best way to learn.
- Patients: BE KIND. Challenge your colleague just enough to facilitate learning a new skill.

Triad Role **Play**

- Patient: *Think of a patient with chronic pain with whom you have struggled (but not TOO much struggle)*
- Provider: *Interview your patient, looking for pain perception and relevant life events. Notice your own reactions.*
- Observer: *Notice when the provider connects empathically with the patient, when the patient appears to feel heard or seen.*

How did that go?

- What was hard about this?

How did that go?

- What was hard about this?
- What did you hear the patient say that you didn't expect?

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- What was hard about this?
- What did you hear the patient say that you didn't expect?
- What did the provider share that creatively made a connection?

How did that go?

- What was hard about this?
- What did you hear the patient say that you didn't expect?
- What did the provider share that creatively made a connection?
- What new insights do you have about caring for your patients?

Summary

- It ain't easy to treat chronic pain - but you can do it!
- Your ongoing patient relationship is the foundation for building trust and hope.
- Careful questioning about the emotional components of pain allows you to create a therapeutic bond, affirming patient resiliency and mitigating your burn out.
- The interview is the intervention!

Questions/ Comments?

Thank you for joining us and participating!

Understanding Definitions of Work – Making Sense of Disability

April 12, 2019

Nels Carlson, MD

- Assistant Dean, Continuing Professional Development
- Associate Professor, Physical Medicine and Rehabilitation
  - No disclosures

Session Objectives

- Understand strength ratings of occupations
- Understand definitions of frequency
- Recognize why having a conversation with the patient regarding disability is important

Unfit for Work - The startling rise of disability in America

Chana Joffe-Walt, NPR 2013

- In the past three decades, the number of Americans who are on disability has skyrocketed.
- The rise has come even as medical advances have allowed many more people to remain on the job, and new laws have banned workplace discrimination against the disabled.
- Every month, 14 million people now get a disability check from the government.

Unfit for Work - The startling rise of disability in America

Chana Joffe-Walt, NPR 2013

- In Hale County, Alabama, nearly 1 in 4 working-age adults is on disability. Sonny Ryan, a retired judge in town, didn't hear disability cases in his courtroom. But the subject came up often. He described one exchange he had with a man who was on disability but looked healthy.
  - "Just out of curiosity, what is your disability?" the judge asked from the bench.
  - "I have high blood pressure," the man said.
  - "So do I," the judge said. "What else?“
  - "I have diabetes.“
  - "So do I."

Unfit for Work - The startling rise of disability in America

Chana Joffe-Walt, NPR 2013

- There's no diagnosis called disability.
- You don't go to the doctor and the doctor says, "We've run the tests and it looks like you have disability."
- It's squishy enough that you can end up with one person with high blood pressure who is labeled disabled and another who is not.

Unfit for Work - The startling rise of disability in America

Chana Joffe-Walt, NPR 2013

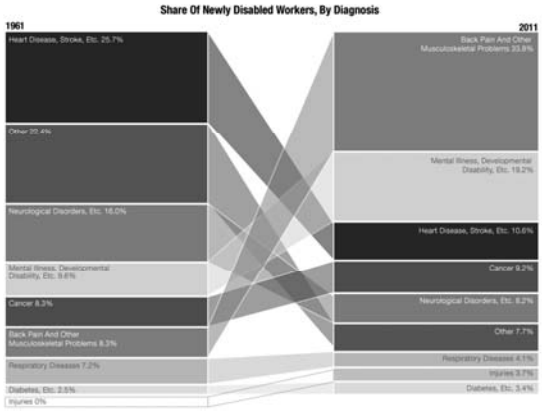
- People don't seem to be faking this pain, but it gets confusing.
- I have back pain. My editor has a herniated disc, and he works harder than anyone I know.
- There must be millions of people with asthma and diabetes who go to work every day.
- Who gets to decide whether, say, back pain makes someone disabled?

Unfit for Work - The startling rise of disability in America
Chana Joffe-Walt, NPR 2013

- You do!

- As far as the federal government is concerned, you're disabled if you have a medical condition that makes it impossible to work.
- In practice, **it's a judgment call made in doctors' offices** and courtrooms around the country.
- The health problems where there is most latitude for judgment -- back pain, mental illness -- are among the fastest growing causes of disability.

Unfit for Work - The startling rise of disability in America
Chana Joffe-Walt, NPR 2013



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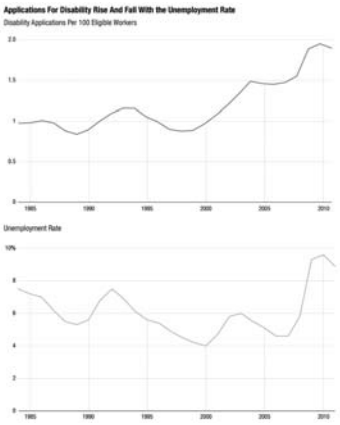

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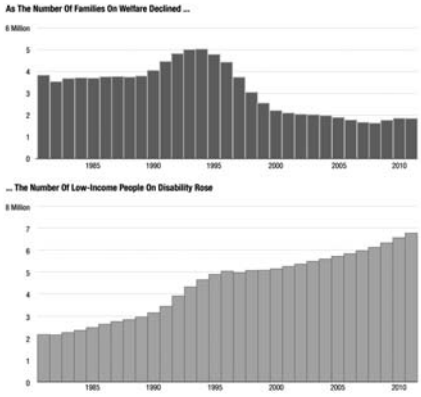

Let's review - why are we talking about this?

- **It impacts us!**

- As far as the federal government is concerned, you're disabled if you have a medical condition that makes it impossible to work.
- **It's a judgment call made in doctors' offices** around the country.
- The health problems where there is most latitude for judgment -- back pain, mental illness -- are among the fastest growing causes of disability.

Dictionary of Occupational Titles

It is a standard reference in several types of cases adjudicated by the Office of Administrative Law Judges
Created by the Employment and Training Administration.

Strength Ratings (Lift, Carry, Push, Pull)

- Sedentary
  - 10# O
  - Stand/walk O or less
- Light
  - 20# O, 10# F
  - Stand/walk F or C
  - Production rate pace
- Medium
  - 20-50# O, 10-25# F, 10# C
- Heavy
  - 50-100# O, 25-50# F, 10-20# C
- Very Heavy
  - >100# O, >50# F, >20# C

Frequency (Material handling, Sit/Stand/Walk)

- Occasional (O)
  - 0-33% of time
  - 1-100 daily reps
- Frequent (F)
  - 34-66% of time
  - 100-500 daily reps
- Constant (C)
  - 67-100% of time
  - >500 daily reps

Clicker Questions
- what are we currently doing?

Level of work?

A. Sedentary
B. Light
C. Medium
D. Heavy
E. Very Heavy

Clicker Questions
- what is the patient able to do?

Work or no work?

A. Able to work
B. Disabled (permanently)
C. Disabled (temporarily)

Level of work?

A. Sedentary
B. Light
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CC – ***

Medical History

- ***

Work/Social History

- ***

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The main concepts from this session are:

Whether we as providers like it or not, we will be asked by our patients to fill out disability paperwork

- Understand strength ratings of occupations
- Understand definitions of frequency
- Recognize why having a conversation with the patient regarding disability is important

Approach to patient with cognitive decline

Deniz Erten-Lyons, MD

April 2018

Goals

- Describe cognitive changes associated with normal aging, mild cognitive impairment and dementia
- Review initial assessment of patient presenting with cognitive decline
- Review treatment options and clinical management for persons with dementia

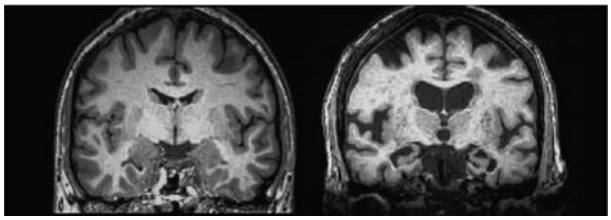
Patient with cognitive complaints

- Normal Aging
- Mild Cognitive Impairment
- Dementia

The aging brain

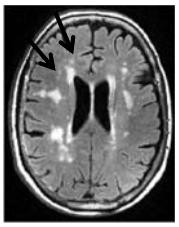
27 year old brain

87 year old brain



Structural brain changes in aging: white matter changes

White matter lesions are very common in the aging brain, up to 90% prevalence >60 years old



Depression

Gait Impairment

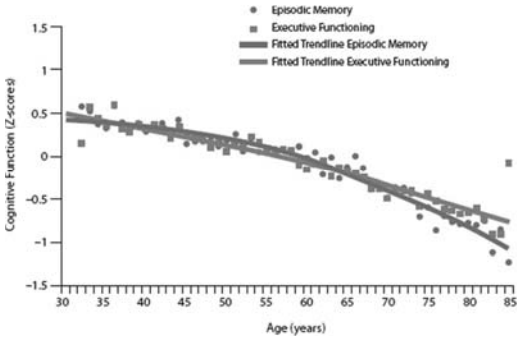
Executive Impairment

De Leeuw et al., J Neurol Neurosurg Psychiatry 2001;**70**:9-14

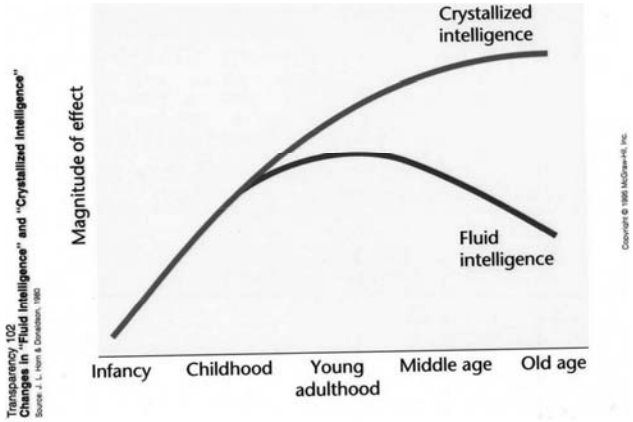
Memory complaints in older adults

Midlife in the United States Study:

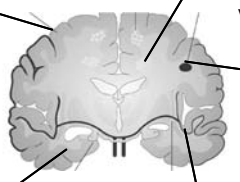
Cognitive function by age



Lahman et al, 2014



Conditions that can cause brain injury



Shrinkage of the cortex
Stroke
Low oxygen
Sleep apnea
Diabetes
Head trauma
Heart failure
High blood pressure

White matter changes
High blood pressure
Diabetes
Heart failure
Kidney or liver disease
Thyroid disease
Vitamin B12 deficiency

Small strokes (lacunar infarcts)
Diabetes
Hypertension
High cholesterol

Hippocampal shrinkage
Scarring of the hippocampus
Low oxygen
Depression and Stress
High blood pressure

Reduced blood flow
Diabetes
Hypertension
High cholesterol
Smoking

Adopted from: Fotuhi, M. *et al.* (2009) Changing perspectives regarding late-life dementia *Nat. Rev. Neurol.* doi:10.1038 nrneurol.2009.175

Patient with cognitive complaints

- Normal Aging
- Mild Cognitive Impairment
- Dementia

} Assessing cognitive function

Diagnostic Evaluation Clinical Practice Guidelines

- Individuals with reported changes in cognition, behavior or function should be evaluated, not dismissed as "normal aging"
- Always, also involve a care partner
- Establish presence and characteristics of changes
- Investigate causes and contributing factors for diagnosis
- Educate, communicate findings and diagnosis, and ensure ongoing management, care and support.

Alzheimer's Association Diagnostic Evaluation Clinical Practice Guideline Workgroup

Benefits of cognitive assessment

- Planning for the future
- Treatment for reversible causes
- Support and education
- Safety issues

Brief screening tests for dementia

- MiniCog: sensitivity (76%) specificity (89%).
- SLUMS-Sensitivity and specificity were both high (98% to 100%)
- MOCA-sensitivity (94% to 100%) specificity (35% to 50%)

Kansagara, Devan and Michele Freeman. "A Systematic Evidence Review of the Signs and Symptoms of Dementia and Brief Cognitive Tests Available in VA." (2010).

Mild Cognitive Impairment (Mild Neurocognitive Disorder)

- Concern for change in cognition
- Objective impairment in ≥ 1 cognitive domains
- Preserved independence in functional abilities
- 2.8% - 20% annual progression to dementia

NIA/AA new diagnostic guidelines for Alzheimer's disease, 2011
American Psychiatric Association, DSM-5, American Psychiatric Association, Arlington 2013.

MCI and Dementia Risk

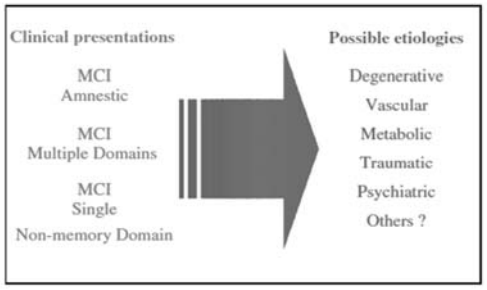


Fig. 1 Heterogeneity of the clinical presentation of mild cognitive impairment (MCI) and potential multiple aetiologies.

Winblad, et al. J of Int. Med. 2004, vol 256,: 240-246

Dementia (Major Neurocognitive Disorder)

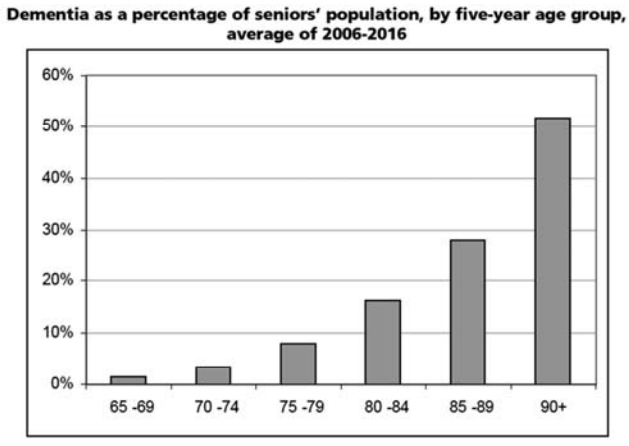
- A decline in cognition involving one or more cognitive domain
- A decline from previous level of function
- Severe enough to interfere with daily function and independence

NIA/AA new diagnostic guidelines for Alzheimer's disease, 2011
American Psychiatric Association, DSM-5, American Psychiatric Association, Arlington 2013.

Prevalence of dementia

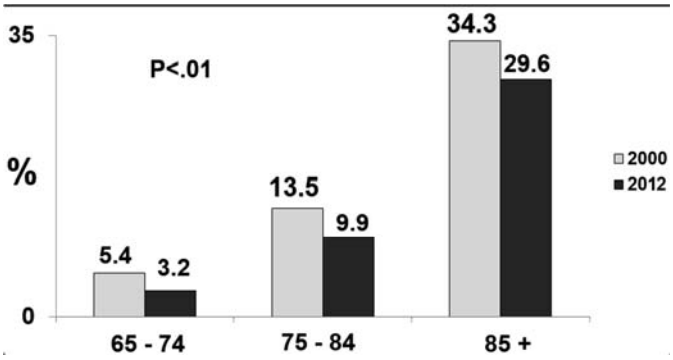
- Worldwide an estimated 50 million people have dementia
- In the United States ~5.7 million people have dementia

WHO, 2017
Alzheimer's Association, 2018



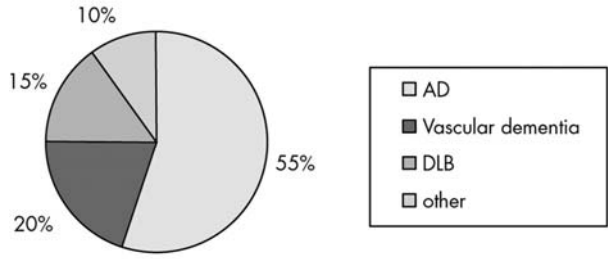
Dementia prevalence projections – LHINs- Alzheimer Society of Ontario

Dementia prevalence by age



NIH/NIA, Langa et al,, JAMA 2017

Approximate relative frequencies of the dementias.



S Cooper, and J D W Greene J Neurol Neurosurg Psychiatry 2005;76:v15-v24

JNNP

Dementia Case Reviews

Dementia work up

Eliminate potentially treatable etiologies:

Drug/medication toxicity
Emotional illness (e.g., severe depression)
Metabolic/endocrine disorders (e.g., thyroid)
Eye/ear/environment
Nutritional (e.g., B_{12} deficiency)
Tumors
Infection
Alcoholism

Brain imaging: CT or MRI of the brain

Reversible labs:
- B12, THS, RPR (if indicated), CBC, CMP, liver function
- Other tests as needed

Alzheimer's Disease

- Insidious onset with slow progressive decline over time
- Short term memory loss initially
- Language and visual-spatial skills affected early
- Change in instrumental activities of daily living, later activities of daily living.
- Prognosis: Usual time between onset and death about 8-12 years

Disclose diagnosis of AD

Early Awareness of Alzheimer Disease
A Neurologist's Personal Perspective

Maintaining quality of life

- Early stage
  - Assess and treat depression
  - Maintain normal activities (exercise, social contacts, hobbies)
  - Discuss values/preferences for Advance Directives
  - Power of attorney
  - Provide preventive care, brain healthy lifestyle
  - Address safety concerns (driving, tools, firearms)
- Middle
  - Consider community referrals: home care, daycare, respite
  - Behavior management
- Late
  - Assess living situation and consider hospice care

Pharmacological treatment

- Cholinesterase inhibitors
  - Donepezil
  - Rivastigmine
  - Galantamine
- NMDA-antagonist

First line treatment for AD: cholinesterase inhibitors

- Inhibit the breakdown of acetylcholine
- No difference in efficacy
- Considered a standard of care
- Modest improvement in roughly half of the patients
- Side effects: GI (nausea & diarrhea), light-headedness, bradycardia, syncope, muscle cramps; caution if h/o bleeding ulcer
- Difference in dosing and side effect profile.

*Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2006, Kazmierski et al, Am J Alzheimers Dis Other Demen. 2018

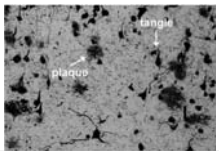
Medications for Alzheimer's disease: memantine

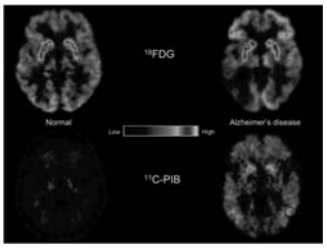
- NMDA receptor antagonist
- May prevent excitatory neurotoxicity from L-glutamate
- Meta-analysis of nine trials (8 funded by pharma) (sample size of 2433)
  - beneficial effect on cognition, behavior, activities of daily living, and global function, but effect size so small that clinical benefit unclear.

Matsunaga et al, PLoS One 2015; 10(4)

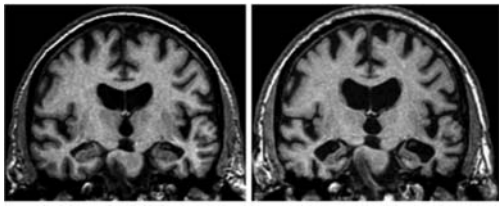
Alzheimer's Disease Biomarkers

- Progressive neurodegenerative brain disease
- Amyloid-rich senile plaques ⟵ PET, CSF
- Neurofibrillary tangles ⟵ CSF
- Neuronal degeneration ⟵ FDG PET, structural MRI
- May be present years before onset of clinical symptoms

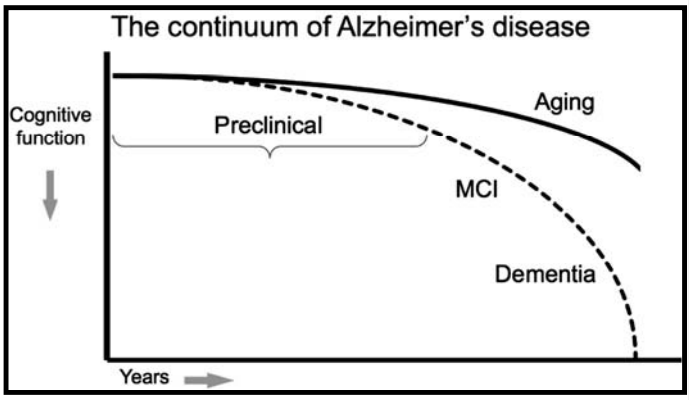




FDG showing reduced activity
C-PIB showing increased amyloid



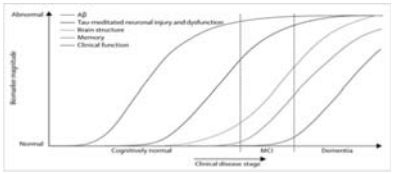
Structural MRI showing atrophy, especially prominent in the medial temporal horns



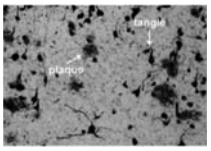
Alzheimer's disease emerging therapies

Disease modifying treatments (ie: anti-amyloid antibodies)
- To prevent tissue damage
- Early treatment

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

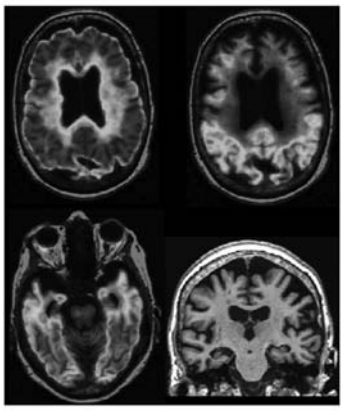


AD pathology



Jack et al, Lancet Neurology, 2010, 9(1):119-128

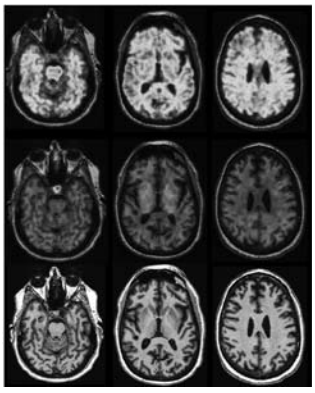
Alzheimer's disease emerging therapies



Alzheimer's disease with dementia. A 75-year-old woman with amnestic multidomain dementia. Participant in the Mayo Alzheimer's Disease Research Center. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom right). Biomarker profile A+T+(N)+.

Alzheimers Dement. Author manuscript; available in PMC 2018 May 18.

Alzheimer's disease emerging therapies

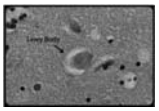


Preclinical Alzheimer's pathologic change. A cognitively unimpaired 67-year-old man. Participant in the Mayo Clinic Study of Aging. Abnormal amyloid PET (Pittsburgh compound B, top row), no uptake on tau PET (with flortaucipir, middle row), no atrophy on MRI (bottom row). Biomarker profile A+T−(N)−.

Alzheimers Dement. Author manuscript; available in PMC 2018 May 18.

Alzheimer's disease emerging therapies

- Anti-amyloid therapies in late-onset AD
  - Bapineuzumab-failed
  - Solanezumab-failed
  - Aducanumab-failed
  - Ongoing: BAN2401
  - Ongoing A4 study-preclinical AD
  - DIAN study-early onset autosomal dominant AD
- Anti-tau study



Dementia with Lewy Bodies

- Features
  - Dementia (preceding parkinsonism)
  - Parkinsonism (rigidity & bradykinesia > tremor)
  - Marked fluctuations in cognition
  - Hallucinations (visual 93%, auditory 50%)
  - Visuospatial and executive dysfunction> memory
  - REM sleep behavior disorder
- Parkinsonism poorly responsive to levodopa
- Pathology: α-synuclein

McKeith et al. Neurology 2005;65

Revised McKeith Criteria for Lewy Body Dementia-2017

Core Clinical Criteria:
Fluctuating cognition
Recurrent visual hallucinations that are typically well formed and detailed
REM Sleep Behavior Disorder
Spontaneous features of parkinsonism

Supportive Clinical Features:
Antipsychotic sensitivity, postural instability, falls, syncope, transient episodes of unresponsiveness, severe autonomic dysfunction, hallucinations in other modalities, anxiety, depression, delusions.

Indicative Biomarkers:
DAT scan, MIBG myocardial scintigraphy, Polysomnographic confirmation of REM sleep behavior

Supportive Biomarkers:
Relative preservation of medial temporal lobe structures, PET scan reduced occipital and cingulate island.
Prominent posterior slow wave activity on EEG.

Treatment for LBD

- Cholinesterase inhibitors: greater cholinergic deficiency
- Memantine
- Behavioral symptom treatment

Londos. Neurol Ther. 2018 Jun; 7(1): 13–22.

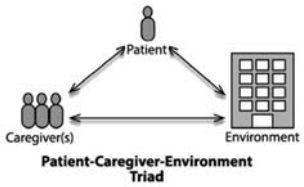
Common behavioral changes in dementia

- Anxiety
- Psychotic symptoms
- Restlessness
- Sleep disturbances
- Wandering
- Agitation
- Aggression
- Depression

Approach to behavior changes

- Describe **
- Investigat e
- Create
- Evaluate

** ASSESS RISK



Patient-Caregiver-Environment Triad

Continuum (Minneap Minn) 2016;22(2):600–614

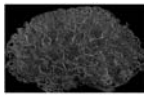
Non-pharmacologic interventions

- Provide quiet, cheerful & familiar environment
- Soft music and lighting
- Provide undemanding social interaction (e.g., reminiscence therapy)
- Encourage exercise & pleasant activities
- Minimize napping
- Distract & redirect rather than arguing

Pharmacological Treatment for Behavior Symptoms

- No FDA approved treatment
- Use medications with **highest benefit to risk ratio**
  - Dementia medications -first line, non-severe symptoms
  - Antidepressants- for agitation, irritability, pacing, compulsive behavior, depression
  - Antipsychotics (higher risk)-first line for psychotic symptoms
    - Avoid risperidone, olanzapine, haldol, aripiprazole in Lewy body dementia (consider quitiapine or clozapine)
  - Mood Stabilizers & antiepileptic
    - Valproic acid, gabapentin
  - Other-prazosin

Vascular cognitive impairment/dementia



- Temporally related to CVA,
- Persist 3 months after stroke
- Abrupt onset with fluctuating, step wise
- May be gradual onset
- Focal neurologic signs
- Vascular lesions on brain imaging
- Cognitive domains: speed of information processing, complex attention and/or frontal-executive functioning
- Gait impairment, urinary incontinence

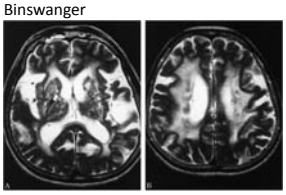
Roman et al, Neurology 1993, Sachdev et al, Alzheimer Dis Assoc Disord. 2014

Vascular Dementia

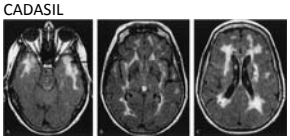
- Cerebrovascular disease on neuroimaging
  - Multiple large vessel infarcts
  - Single strategic infarct
  - Multiple basal ganglia infarcts
  - Extensive white matter disease

Strategic Infarct

Binswanger



CADASIL



Frontotemporal Dementias

- Fourth most common cause of dementia
- Age at onset 35-75
- Duration 3-17 years (mean 8)
- 20-40% have a family history
- Subtypes:
  - Behavior variant
  - Language variant
    - Semantic dementia
    - Nonfluent/agrammatic variant

Rapidly Progressive Dementias

- Rapid cognitive and functional decline over weeks or months
- Infectious (HIV, CJD, viral)
- Autoimmune
- Paraneoplastic
- Neoplastic
- Iatrogenic
- Systemic Disease
- Atypical presentations of AD, FTD, DLB, others

Take home points

- Diagnosing MCI or dementia
- Defining and recognizing type of dementia
- Initiating treatment and counseling
- Referral to specialist if deemed necessary

Resources

- American Academy of Family Physicians Cognitive Care Kit
- Alzheimer's Association Cognitive Assessment Toolkit
- Questions to me: ertenlyo@ohsu.edu

Contemporary Management of Dyslipidemia

26th OHSU Annual INTERNAL MEDICINE REVIEW
April 12, 2019

Cezary Wójcik MD, PhD, DSc, FNLA
Assistant Professor of Family Medicine, OHSU
Diplomate, American Board of Clinical Lipidology

Part 1 – The new 2018 cholesterol guideline

Part 2 – Implications of REDUCE-IT trial

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA

Guideline on the Management of Blood Cholesterol

2018 Cholesterol Guideline

- In all individuals, emphasize a heart-healthy lifestyle across the life course.
- A healthy lifestyle reduces ASCVD risk at all ages.
- In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction.
- In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion and emphasizes intensive lifestyle efforts.
- In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.

2018 Cholesterol Guideline – General Concepts

	2013 Guideline	2018 Guideline
Organizations on the guideline writing committee	ACC and AHA	12 organizations
Population	Adults	Adults, children and adolescents
	Distinct risk for blacks and for Caucasians	Focus on special populations, including more ethnic and racial groups

2018 Cholesterol Guideline – General Concepts

	2013 Guideline	2018 Guideline
Screening laboratory testing	Fasting lipid panel	Non-fasting lipid panel is allowed for most patient groups for initial screening and ASCVD risk estimation
Patient involvement	Recommended conducting a physician–patient risk discussion to consider the potential for ASCVD risk reduction with statin therapy	Continues and expands on use of shared decision-making in the form of the physician–patient risk discussion
Value statement	None	Included for PCSK9 inhibitors

2018 Cholesterol Guideline – General Concepts

	2013 Guideline	2018 Guideline
Treatment effectiveness and adherence	High- and moderate-intensity statin therapy recommendations did not specify LDL-C reduction targets but did recommend follow-up LDL-C testing for adherence to gauge adequacy of statin effect	Specifies importance of percentage reduction in LDL-C level when prescribing high (≥50%) or moderate- intensity (30%-49%) statin therapy as well as follow-up LDL-C testing for adherence and to gauge effects of LDL-C lowering medication.

Monitoring in Response to LDL-C–Lowering Therapy

Recommendation for Monitoring		
COR	**LOE**	**Recommendation**
I	**A**	**Adherence to changes in lifestyle and effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety.**

2018 Cholesterol Guideline – General Concepts

	2013 Guideline	2018 Guideline
Lipid thresholds for addition of non-statin therapy	None	LDL-C and non-HDL-C thresholds are introduced for different prevention groups

Target – LDL-C, Non-HDL-C, Systolic BP etc.

Goal – Titrating therapy to achieve a certain target level (e.g. LDL-C < 70 mg/dL)

Threshold – Target level at which an additional intervention is indicated (e.g. LDL-C > 70 mg/dL)

2018 Cholesterol Guideline

Secondary Prevention

2018 Cholesterol Guideline – Secondary Prevention

	2013 Guideline	2018 Guideline
Very high-risk category of ASCVD	No equivalent recommendation	Adds specific recommendations for very high-risk patients

Very high risk: multiple major ASCVD events or 1 major ASCVD event plus multiple high risk conditions

Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

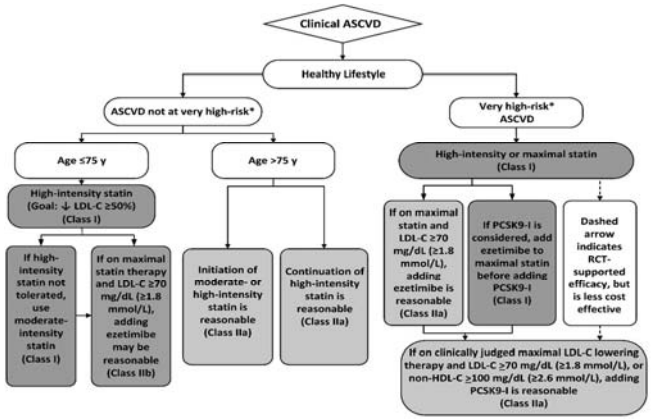
*multiple major ASCVD events or 1 major ASCVD event plus multiple high risk conditions

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

2018 Cholesterol Guideline – Secondary Prevention

	2013 Guideline	2018 Guideline
Non-statin therapy	Consider adding non-statin therapy in adults at higher risk of ASCVD who are receiving maximally tolerated statin therapy with a less-than-anticipated therapeutic response	Adds specific recommendations for very high-risk patients
	Use non-statin cholesterol-lowering drugs in adults who are a candidate for statin therapy but are completely statin-intolerant	Very high-risk ASCVD patients should receive maximally tolerated statin therapy; if the LDL-C level remains ≥70 mg/dL, add ezetimibe before considering a PCSK9 inhibitor. If, despite ezetimibe, the LDL-C level is ≥70 mg/dL or non-HDL-C is ≥100 mg/dL, consider a PCSK9 inhibitor

Secondary Prevention



2018 Cholesterol Guideline

Primary Prevention

2018 Cholesterol Guideline – Primary Prevention

	2013 Guideline	2018 Guideline
Use of pooled cohort equations for risk assessment	Classified adults as: low risk (<5%) borderline risk (5% to <7.5%) high risk (≥7.5%)	Adds intermediate risk (≥7.5 to <20%) category and new definition of high risk (≥20%) No change in low and borderline risk definitions
Statin therapy	Moderate- or high-intensity statin therapy for adults whose 10-year ASCVD risk is ≥7.5%	Moderate-intensity statin therapy for adults at intermediate risk (≥7.5–<20%) Maximally tolerated or high-intensity statin therapy for adults at high risk (≥20%)

2018 Cholesterol Guideline – Primary Prevention

	2013 Guideline	2018 Guideline
Risk-enhancing factors	No equivalent recommendation	Allows identification of patients at low and intermediate risk who would benefit most from statin therapy

Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors

- **Family history of premature ASCVD** (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m² with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
- **High-risk race/ethnicities** (e.g., South Asian ancestry)

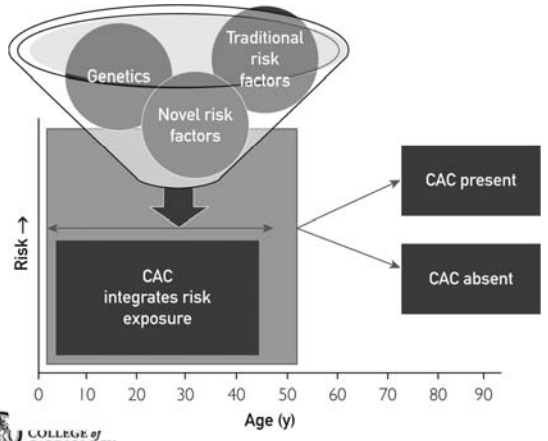
Risk-Enhancing Factors

- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL);
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    - **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
    - **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
    - **ABI** <0.9

2018 Cholesterol Guideline – Primary Prevention

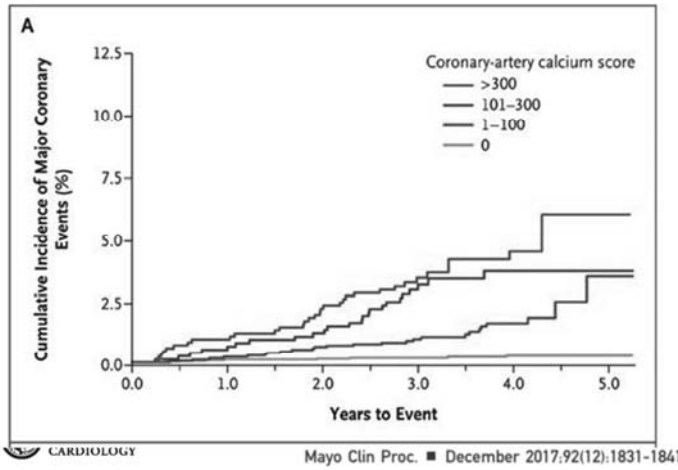
	2013 Guideline	2018 Guideline
Coronary Artery Calcium (CAC)	One of several factors that can be considered to inform treatment decisions (ie, a CAC score ≥300 or ≥75th percentile for age, sex, and ethnicity)	Used in select adults if a risk-based treatment decision regarding initiation of statin therapy is uncertain after reviewing risk enhancing factors (CAC> 0 is significant, especially when > 100)
		In selected intermediate risk patients, CAC score = 0 can be useful in the decision to withhold or postpone statin therapy unless higher-risk conditions are present

CORONARY CALCIUM SCORING



Mayo Clin Proc. ■ December 2017;92(12):1831-1841

CORONARY CALCIUM SCORING



Mayo Clin Proc. ■ December 2017;92(12):1831-1841

Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7–4.8 mmol/L)

COR	LOE	Recommendations
IIa	B-NR	**In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND** **•If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking);** **•If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age;** **•If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy.**

2018 Cholesterol Guideline – Primary Prevention

	2013 Guideline	2018 Guideline
Non-statin therapy	No equivalent recommendation	Ezetimibe or a bile-acid sequestrant (if TG < 300 mg/dL) can be considered for adults at intermediate risk who would benefit from more aggressive LDL-C lowering but in whom high-intensity statin therapy is not tolerated

2018 Cholesterol Guideline

Severe Hypercholesterolemia

2018 Cholesterol Guideline – Severe hypercholesterolemia

	2013 Guideline	2018 Guideline
Non-statin therapy	For adults 21-75 year old who have an LDL-C level ≥190 mg/ dL after maximizing statin therapy, adding a non-statin drug can be considered to further lower the LDL-C level	Prescribe ezetimibe in patients 20-75 year old who have an LDL-C level ≥190 mg/dL and who 1) achieve a <50% reduction in LDL-C while receiving maximally tolerated statin therapy or 2) who have an LDL-C level ≥100 mg/dL (or both)

2018 Cholesterol Guideline – Severe hypercholesterolemia

	2013 Guideline	2018 Guideline
Non-statin therapy		Prescribe a PCSK9 inhibitor in patients who 1) have a baseline LDL-C level ≥220 mg/dL and 2) achieve an on-treatment LDL-C level ≥130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy

2018 Cholesterol Guideline – Severe hypercholesterolemia

	2013 Guideline	2018 Guideline
Non-statin therapy		Prescribe a PCSK9 inhibitor in patients 30-75 y who have 1) heterozygous familial hypercholesterolemia and 2) an LDL-C level ≥100 mg/dL while taking maximally tolerated statin and ezetimibe therapy

2018 Cholesterol Guideline

Diabetes Mellitus

2018 Cholesterol Guideline – Diabetes

	2013 Guideline	2018 Guideline
Adults 40 to 75 years of age with DM	Moderate-intensity statin	Moderate-intensity statin
	High-intensity statin when ≥7.5% estimated 10-year ASCVD risk unless contraindicated	High intensity statin when multiple ASCVD risk factors are present Reasonable to add ezetimibe when ≥20% estimated 10-year ASCVD risk

2018 Cholesterol Guideline – Diabetes

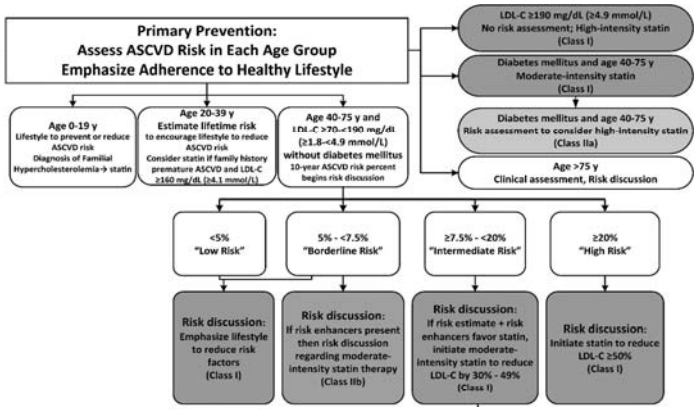
	2013 Guideline	2018 Guideline
Adults > 75 years of age with DM	It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy	If they are already on statin therapy, it is reasonable to continue statin therapy It may be reasonable to initiate statin therapy

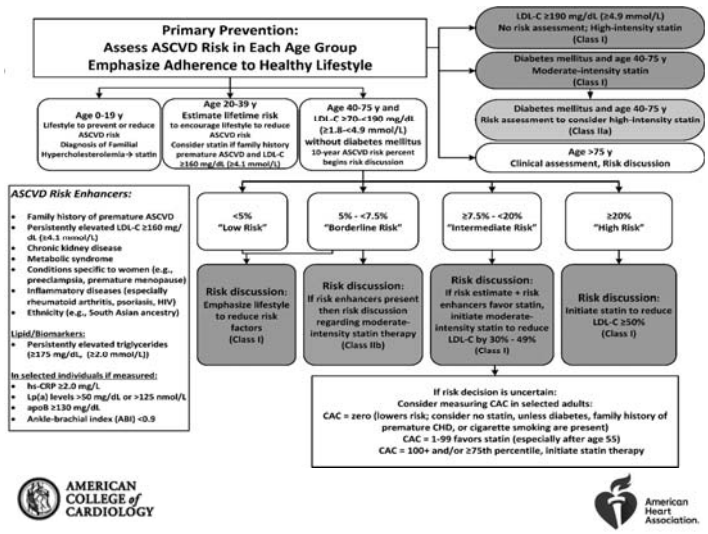
2018 Cholesterol Guideline – Diabetes

	2013 Guideline	2018 Guideline
Adults < 40 years of age with DM	It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy	If DM is either of long duration (≥10 years of T2DM, ≥20 years of T1DM), albuminuria (≥30 mcg of albumin/mg creatinine), eGFR < 60 mL/min/1.73 m^2, retinopathy, neuropathy, or ABI; <0.9, it may be reasonable to initiate statin therapy.

Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
• Long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus) • Albuminuria ≥30 mcg of albumin/mg creatinine • eGFR <60 mL/min/1.73 m^2 • Retinopathy • Neuropathy • ABI <0.9





Primary Prevention in Older Adults

2013 Guideline	2018 Guideline
Initiation of statins for primary prevention of ASCVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care. A discussion of the potential ASCVD risk reduction benefits, risk of adverse effects, drug-drug interaction, and patient preferences precede the initiation of statin therapy for primary prevention in older individuals.	In adults >75 years of age with an LDL-C level of 70 to 189 mg/dL initiating a moderate-intensity statin may be reasonable. It may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy. In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy.

Issues Specific to Women

Recommendations for Issues Specific to Women		
COR	**LOE**	**Recommendations**
I	**B-NR**	**Clinicians should consider conditions specific to women, such as premature menopause (age <40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes mellitus, small-for-gestational-age infants, preterm deliveries), when discussing lifestyle intervention and the potential for benefit of statin therapy.**
I	**C-LD**	**Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception.**
I	**C-LD**	**Women of childbearing age with hypercholesterolemia who plan to become pregnant should stop the statin 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered.**

Adults With Chronic Kidney Disease

Recommendations for Adults With CKD		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who are at 10-year ASCVD risk of 7.5% or higher, CKD not treated with dialysis or kidney transplantation is a risk-enhancing factor and initiation of a moderate-intensity statin or moderate-intensity statins combined with ezetimibe can be useful.**
IIb	**C-LD**	**In adults with advanced kidney disease that requires dialysis treatment who are currently on LDL-lowering therapy with a statin, it may be reasonable to continue the statin.**
III: No Benefit	**B-R**	**In adults with advanced kidney disease who require dialysis treatment, initiation of a statin is not recommended.**

Adults With Chronic Inflammatory Disorders and HIV

Recommendations for Adults With Chronic Inflammatory Disorders and HIV		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who have a 10-year ASCVD risk of 7.5% or higher, chronic inflammatory disorders and HIV are risk-enhancing factors and in risk discussion favor moderate-intensity statin therapy or high-intensity statin therapy.**
IIa	**B-NR**	**In patients with chronic inflammatory disorders or HIV, a fasting lipid profile and assessment of ASCVD risk factors can be useful as a) a guide to benefit of statin therapy and b) for monitoring or adjusting lipid-lowering drug therapy before and 4 to 12 weeks after starting inflammatory disease–modifying therapy or antiretroviral therapy.**
IIa	**B-NR**	**In adults with RA who undergo ASCVD risk assessment with measurement of a lipid profile, it can be useful to recheck lipid values and other major ASCVD risk factors 2 to 4 months after the patient's inflammatory disease has been controlled.**

2018 Cholesterol Guideline – Triglycerides

	2013 Guideline	2018 Guideline
Hypertriglyceridemia	Not addressed	Moderate hypertriglyceridemia (non-fasting or fasting triglyceride level ≥175 mg/dL) is considered a risk-enhancing factor
		Severe hypertriglyceridemia (≥ 500 mg/dL) requires specific therapy to prevent pancreatitis

Hypertriglyceridemia

Recommendations for Hypertriglyceridemia		
COR	**LOE**	**Recommendations**
I	**B-NR**	**In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [1.9 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.**
IIa	**B-R**	**In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy.**

Hypertriglyceridemia

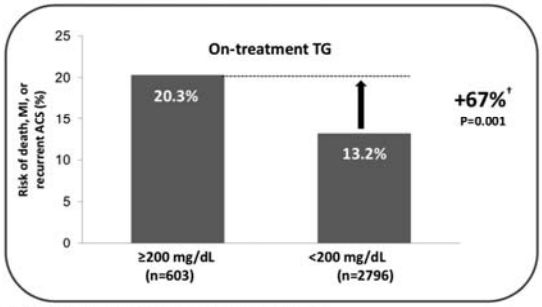
Recommendations for Hypertriglyceridemia		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy.**
IIa	**B-NR**	**In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1000 mg/dL (11.3 mmol/L)), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy.**

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association.

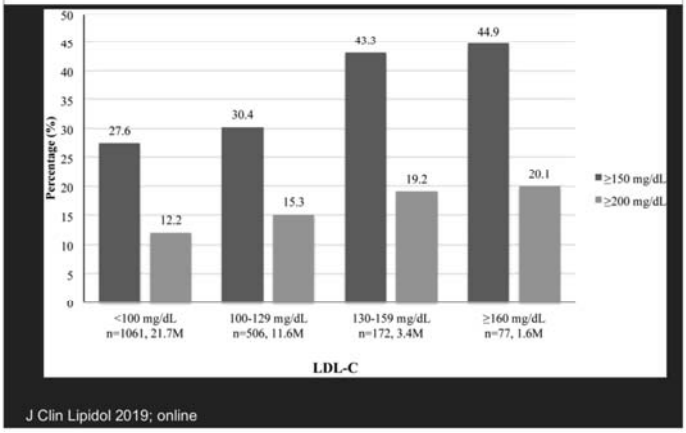
PROVE IT-TIMI 22: Elevated TG Increases Risk of Recurrent Events, Despite LDL-C at Goal

Despite achieving LDL-C <70 mg/dL with a high-dose statin, patients with TG ≥200 mg/dL have a 67% higher risk of coronary events*



*Death, myocardial infarction, or recurrent acute coronary syndrome
†Calculated from adjusted hazard ratio of TG <200 mg/dL (95% CI) = 0.60 (0.45-0.81)
Miller M et al. *J Am Coll Cardiol*. 2008;51:724-30.

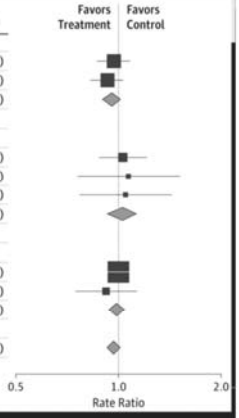
Incidence of High Triglycerides in Statin-treated US Adults: NHANES 2007-2014



J Clin Lipidol 2019; online

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87-1.08)
Coronary heart disease death	1301 (3.3)	1394 (3.6)	0.93 (0.83-1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90-1.01)
			P = .12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88-1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76-1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77-1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93-1.13)
			P = .60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93-1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75-1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94-1.04)
			P = .60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93-1.01)
			P = .10



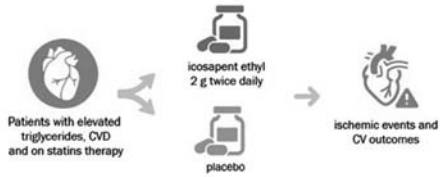
JAMA Cardiol. 2018;3(3):225-233

REDUCE IT: Cardiovascular Risk Reduction With Icosapent Ethyl for Hypertriglyceridemia

Multicenter, randomized, double-blind, placebo-controlled trial

AMERICAN COLLEGE of CARDIOLOGY

Objective: To assess the effects of icosapent ethyl in patients with elevated triglycerides on ischemic events.



6,179 Patients with CVD or with diabetes and other risk factors, on statin therapy and elevated triglyceride levels (135-499 mg/dl) were randomized to

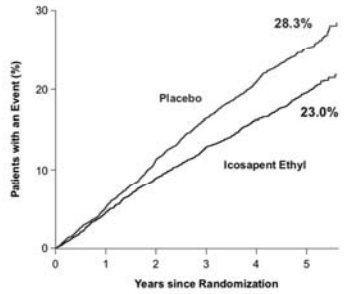
Key Baseline Characteristics

reduce-it

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2019;380:11-22.

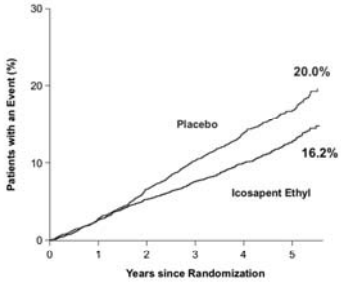
Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019;380:11-22.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

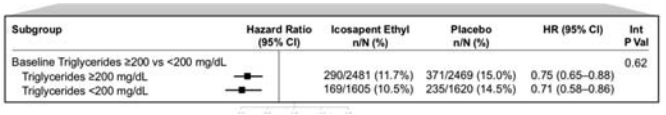
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019;380:11-22.

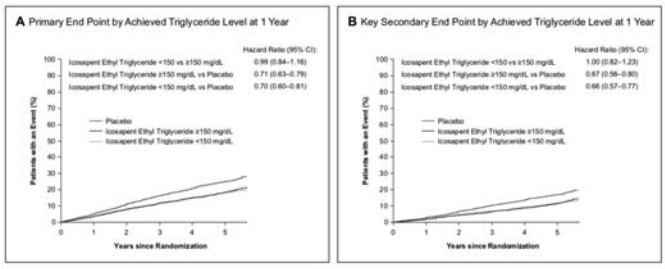
Prespecified Hierarchical Testing

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction		250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization		216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death		174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina		108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke		98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality		274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

0.4 1.0 1.4
Icosapent Ethyl Better Placebo Better
RRR denotes relative risk reduction

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019;380:11-22.





Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019;380:11-22.

How EPA causes this benefit?

- **Could it be solely due to reducing TG by ~ 20% and non-HDL-C by ~ 10%?**

  1.This degree of lipid effect could be reasonably expected to have a 5 –10% benefit, but not a 25% benefit
  2. There could be improvement in postprandial TGRL handling
  3. The use of mineral oil in placebo group increasing LDL-C by 4 mg/dL can not explain the additional benefit

- Could the benefit be related to the postulated benefits of high dose EPA beyond changes in triglycerides/lipoproteins?

  1. Anti-inflammatory (reduced CRP)
  2. Antioxidant
  3. Antithrombotic
  4. Anti-arrhythmic (reduced sudden death, cardiac arrest)

What are the clinical implications of REDUCE-IT?

- Should all ASCVD patients on optimal statin +/- ezetimibe who have a TG > 135 mg/dL be started on EPA 4 gm/day?
- Would patients at high ASCVD risk and TG < 135 mg/dL also benefit?
- OTC omega 3 supplements as well as Rx strength omega3 do not have evidence for ASCVD risk reduction
- Oxidized OTC omega3 preparations may cause harm, also contain significant amount of saturated fat, raising LDL-C
- Currently, icosapent ethyl is only FDA indicated for treatment of TG > 500 mg/dL
- Cost of monthly therapy with online coupon is ~$270 (not an option for Medicaid/Medicare – full price ~$450)

Thank you for your attention!

Please e-mail me with questions at wojcikc@ohsu.edu

If you want to learn more about lipid management consider joining the National Lipid Association (**lipid.org)** and become board certified in clinical lipidology

The Healthy Aging Brain

David Mansoor, MD
Associate Professor of Psychiatry
April 2019

Outline

- What does it mean to age?
  - Perceptions of old age
- Aging effect on the body
  - Physical marks of old age
  - External and internal changes
- Aging effect on the brain
  - Mental marks of old age
  - Structural and cognitive changes
    - Normal aging and pathological states
- Can we change the way our brain ages?

Activity

- What does it mean to be old?

Think of 5 adjectives that can be used to describe aging and getting older

Aging

- Sources of stereotyping
  - Television/Movies/Media
    - Often inaccurate representation as incapable, helpless, grumpy

Aging

- Sources of stereotyping
  - Television/Movies/Media
    - Often inaccurate representatio
      grumpy
  - Language
    - "aged," "elderly," "senior citizen," "gramps, " granny," "older timer," "old folk"

Aging

- Sources of stereotyping
  - Television/Movies/Media
    - Often inaccurate representation as incapable, helpless, grumpy
  - Language
    - "aged," "elderly," "senior citizen," "gramps, " granny," "older timer," "old folk"
  - Advertising
    - Emphasis placed on youth and looking young

Aging

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    - "aged," "elderly," "senior citizen," "gramps, " granny," "older timer," "old folk"
  - Advertising
    - Emphasis placed on youth and looking young
- Older people with positive age stereotypes recover faster from disability

JAMA. 2012;308(19):1972-1973. doi:10.1001/jama.2012.14541

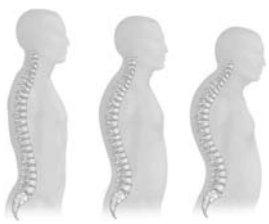
Aging

- There is no universal definition
  - Chronologic age
    - Young old (65 to 74)
    - Middle old (75-84)
    - Oldest old (85+)
  - Psychological and social factors
    - Developmental milestones
  - Biological factors
    - Body and brain

Aging Effects on Body

External Changes

- Wrinkles
- Loss of hair pigment
- Thinning hair
- Changes in mobility
  - Reduced muscle mass
  - Osteoporosis



Internal Changes

- Cardiovascular system
- Respiratory system
- Renal system
- Reproductive system
- Sensory systems
- Accumulation of chronic illness

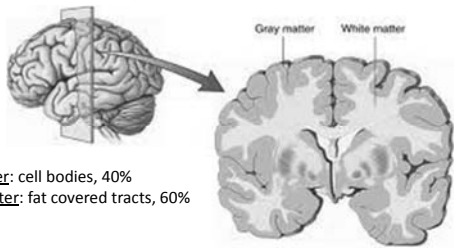
⇨ *"Slowness of behavior" – slowness of reaction and physical performance*
Sensitivity to medications and illness

Aging Effects on the Brain

STRUCTURAL BRAIN CHANGES **COGNITIVE CHANGES**

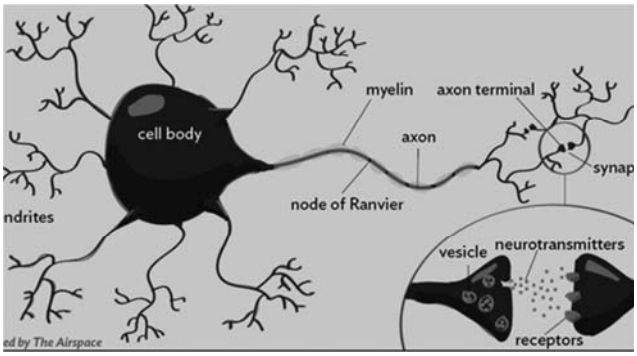
Structural Changes

- Neuroanatomy Review



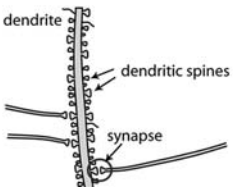
Grey matter: cell bodies, 40%
White matter: fat covered tracts, 60%

Structural Changes



Structural Changes

- Dendritic spines are plastic
  - Shape, volume, number change within seconds to minutes
  - Reinforce neural pathways
    - Play a role in memory and learning
    - The more they're stimulated, the bigger they become
    - The stronger the connection between neurons



⇨ • *The brain changes with experience*

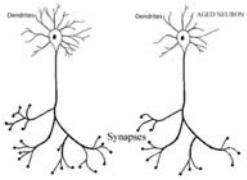
Structural Changes

- From birth to age 3, the brain increases 4 times in weight
- Slower growth through age 19
- Stable until about age 40
- Slow decrease thereafter
- By age 86, it will have reduced by 11% of its weight at age 19

⇨ *Normal brain gets smaller with aging*

Structural Changes

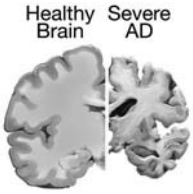
- Grey Matter
  - Constant/linear decline after age 20
  - Reduced length and arborization of dendrites
  - Reduction in spine density (decrease in dendritic synapses)
  - Neuronal cell death
  - Changes are greatest in the frontal lobes
- White matter
  - Volume peaks at age 50, and then begins to decline
  - Deterioration of myelin sheath and oligodendrocyte
  - Susceptible to age related vascular changes
    - Frontal-striatal circuits



⇨ *Signal transmission from axon to axon is decreased*

Structural Changes

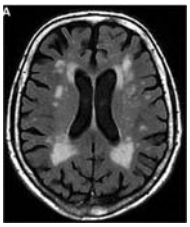
- Pathological States
  - Alzheimer's disease
    - Extracellular deposition of beta amyloid
    - Intracellular deposition of neurofibrillary tangles
    - Medial temporal lobe: memory
    - Greater rate of global atrophy



Neurology 2003; **61:** 487–92

Structural Changes

- Pathological States
  - Age related white matter changes
    - WM changes are prevalent (50-98%)
    - Related to age and vascular risk factors
    - Due to small vessel arteriosclerosis



    - A substrate for cognitive impairment, depression, and functional loss
      - Disrupt cortical-subcortical-cortical connections

Journal of Aging Research Volume 2011,

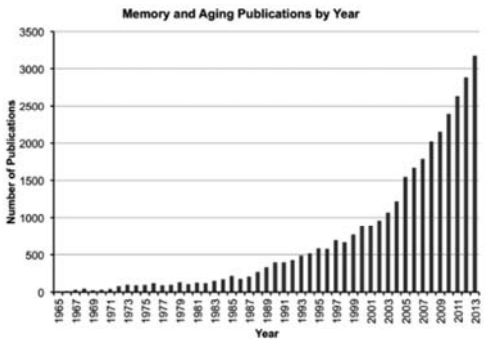
Structural Changes

- Other factors
  - Medications
    - Drowsiness and mental dulling
  - Sensory changes
    - Interfere with processing of information
  - Health related changes
    - Concentration and processing speed
  - Changes in mood

Cognitive Changes

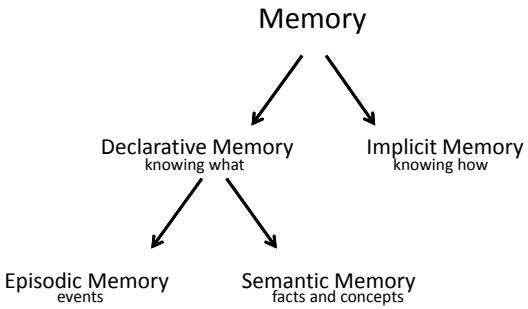
- Cognition: how we absorb stimuli and information, and how we make sense of it
  - Memory
  - Processing speed
  - Attention
  - Executive function
  - Language
  - Visual motor function

Cognitive Changes



Journals of Gerontology: PSYCHOLOGICAL SCIENCES, 2017, Vol. 72, No. 1

Cognitive Changes



Activity

- Semantic Memory vs Episodic Memory vs Procedural Memory

Cognitive Changes: What Stays Stable?

- **<u>Procedural</u> memory**
- **<u>Semantic</u> memory**

- Stable or gradually improves through the sixth and seventh decades of life

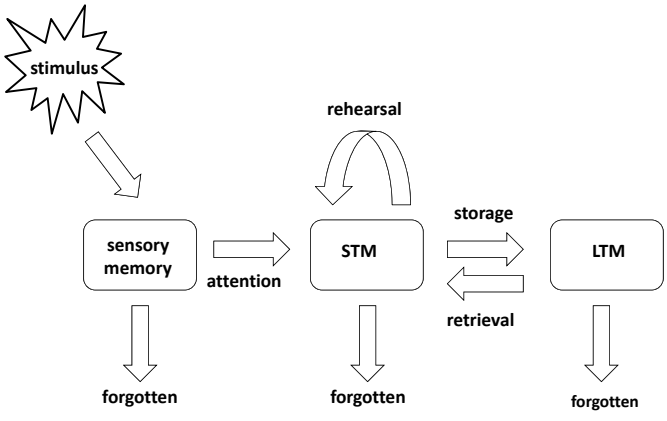
⇨ *Overlearned skills and knowledge*
Accumulation of information based on life experiences
"With Age Comes Wisdom"

Cognitive Changes: What Declines?

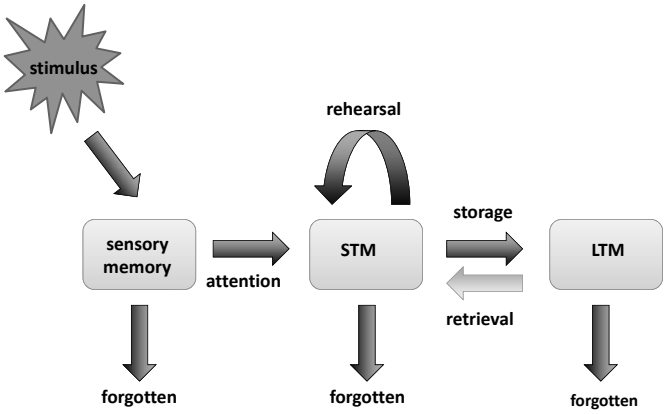
- **<u>Episodic</u> memory**: tend not to do as well on tests of new learning
  - Peaks early and declines linearly after age 40
  - By age 70, the amount of information recalled 30 minutes after hearing a story is 75% of the amount remembered by an 18 year old
    - perform better if given cues

PsychCorp . Wechsler Memory Scale-Fourth Edition (WMS-IV) Technical and Interpretative Manual.San Antonio, TX: Pearson; 2009
Aging Neuropsychol. Cogn., 4 (1997), pp. 1–32

How A Memory Is Formed



How A Memory Is Formed

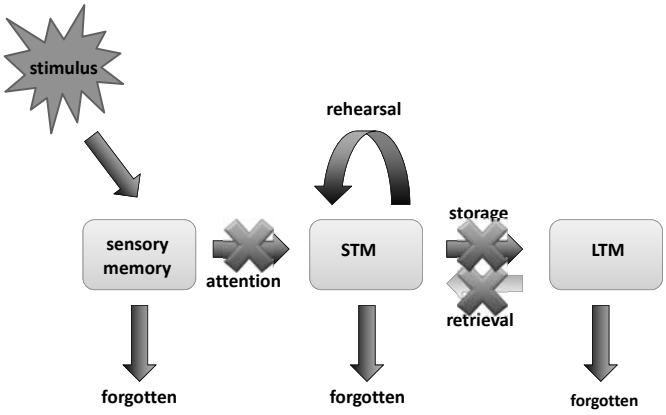


Cognitive Changes: What Declines?

- Episodic memory continued
  - Slow processing speed - rate of acquisition declines
  - Changes in attention
  - A more shallow depth of processing
    - To make something memorable, you have to make it meaningful
  - Retrieval
    - Free recall < cued recall < recognition memory
    - "Tip of the tongue" / "senior moment"
    - Limited strategic search processes, slower processing speed

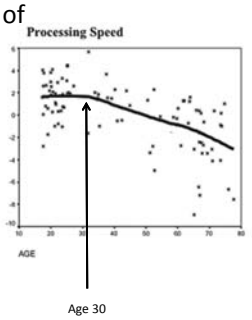
Human Memory and Cognitive Capabilities, Mechanisms and Performances.Elsevier; Amsterdam: 1986.

How A Memory Is Formed



Cognitive Changes: What Declines?

- **Processing speed**
  - The rate that we can take a bit of new information, reach some judgment, and formulate a response
    - Eg, solve problems and make decisions
  - Motor speed: slows with lengthened reaction time



Canadian Geriatrics Journal, Volume 13, 2011

Cognitive Changes: What Declines?

- **Attention**
  - *Sustained* – simple auditory attention span, stable
  - *Selective* – focus on specific information while ignoring irrelevant information, mixed
    - Stroop task

Stroop Task

BLUE	RED	YELLOW
RED	GREEN	GREEN
YELLOW	BLUE	RED

Stroop Task

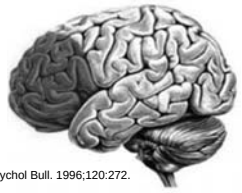
BLUE	RED	YELLOW
RED	GREEN	GREEN
YELLOW	BLUE	RED

Cognitive Changes: What Declines?

- **Attention**
  - *Sustained* – simple auditory attention span, stable
  - *Selective* – focus on specific information while ignoring irrelevant information, mixed
  - *Divided* – focus on multiple tasks simultaneously, declines (particularly for challenging tasks)
- **Working memory** – hold information in memory while simultaneously manipulating it
  - Mental manipulation and reorganization
  - Peaks age 18 to 20 then declines

Cognitive Changes: What Declines?

- **Executive function**
  - Cognitive processes that have to do with managing yourself and your resources in order to achieve a goal
    - Helps us to get stuff done efficiently
    - Sequence, organize, abstract, plan
    - Monitor and regulate behavior
  - Mediated by frontal lobes
    - Greater sensitivity of the prefrontal brain region and its associated cognitive abilities to the aging process



West RL. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull. 1996;120:272.

Crystallized vs Fluid Intelligence

- Crystallized: vocabulary, general knowledge, social judgment, how to do things
  - An accumulation of information based on life experience
  - Skills, abilities, and knowledge that are over-learned, well-practiced, and familiar
  - Peaks later in life, hitting apex at age 60 or 70
- Fluid: problem solving and reasoning about unfamiliar things that are independent of what you've learned
  - Learn and process new information, solve problems, and attend to your environment
  - Peaks in adolescence and begins to decline at age 30-40

Clin Geriatr Med. 2013 November ; 29(4): 737–752

Cognitive Changes: Summary

Decline	Stable	Improve
free recall	implicit memory	semantic memory
episodic memory	recognition	crystallized intelligence
processing speed	sustained attention	
divided attention		
fluid intelligence		

Cognitive Changes: Summary

- Normal cognitive aging
  - Changes are small and should not result in an impairment in function!
  - Older adults are proficient when it comes to situations that require past experience or knowledge
  - When function is impaired, or changes are happening rapidly, we need to determine the cause

"We turn not older with years, but newer every day" – Emily Dickinson

Can We Keep Our Brains Healthy?

- Lifestyle
  - Diet
  - Exercise
  - Socializing
- Cognitive exercises
- Medications
  - Supplements

Lifestyle - Diet

- Mediterranean Diet
  - Plant based foods
    - fruits, nuts, legumes, complex carbohydrates (eg, whole grains)
  - Low consumption of meat and meat products (eg dairy), with the exception of fish
  - Olive oil
  - Red wine (5 to 10 oz / day)

Lifestyle - Diet

- Mediterranean Diet
  - May protect against cognitive decline (along with other age related disorders)
  - Atherosclerosis, mitochondrial dysfunction (oxidative stress), inflammation
    - Reduce LDL and raise HDL
    - Rich source of anti-oxidents (vit E, vit C, folate, polyphenols)
    - Lower inflammatory biomarkers
  - Reduced burden of WM hyperintensities

Arch Neurol. 2012;69(2):251-256
J Alzheimers Dis 2010;**22**:483–92

Lifestyle - Diet

- Mediterranean diet

Randomized clinical trial

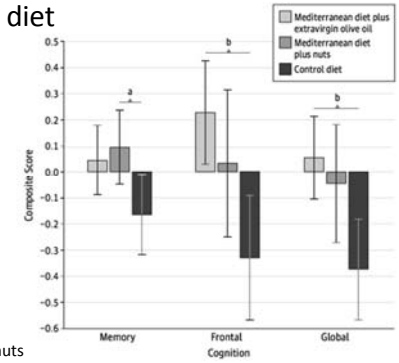
447 patients mean age 66.7 with cardiovascular risk factors

Control: Low fat
Mixed nuts: 30g/day
Olive oil: 1L/week

~4 years, neuropsychological testing

Cognitive change over time

Results: MD supplemented with nuts or olive oil improved cognitive fxn



JAMA Intern Med. 2015;175(7):1094-1103

Lifestyle

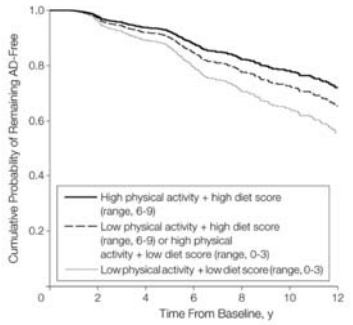
- Mediterranean diet plus exercise

Prospective cohort study

1880 older adults followed over 12 years

The association between physical activity and diet and AD risk

High PA and high diet adherence associated with 35-44% relative risk reduction compared to the low PA and diet group



JAMA. 2009;302(6):627-637.

Lifestyle - Exercise

- Tai-chi: mind/body exercise that incorporates physical, cognitive, social and meditative components
  - "Meditation in motion"
  - Improves age-related decline in cardiovascular health, balance, flexibility, and mood
- RCT, 120 older adults , 40 weeks
  - Tai chi, 50 minutes, 3x/week
  - Socialization, 1 hour, 3x/week
  - Walking 30 minute, 3x/week
  - No intervention
  - Whole brain volume and cognitive function improved

J Alzheimers Dis. 2012 ; 30(4): 757–766

Lifestyle - Exercise

- Like the Mediterranean diet, reduces risk of heart disease, diabetes, and stroke
- Helps improve muscle mass, strength, and aerobic capacity
- Also helps to improve mood and reduce anxiety
- Regular exercise is good!
  - 30 minutes of moderate intensity, 5x per week; tai chi, aerobic, or resistance
- It's never too late to exercise!
  - Starting at age 85 can improve survival benefits at 3 years

Arch Intern Med. 2009;169(16):1476.

Lifestyle - Socialization

- "Blue zones": 5 geographic areas where people live statistically longest
  - Okinawa, Sardinia, Nicoya, Icaria, Loma Linda
  - Social engagement: socially active and integrated into their community
    - Engagement in family life
    - Life purpose
    - Engaged in spirituality or religion
  - Constant physical activity, non-smoking, plant based diet, red wine, legumes, limited meat

Blue Zones, LLC; "The Secrets of a Long Life," *National Geographic Magazine* Nov 2005

Cognitive Exercises

- Learning and mental activity positively cognitive functioning
  - Occupational complexity
  - Level of education
  - Cognitively complex leisure activities (reading, hobbies)
  - An engaged lifestyle (learning a new language or game)
- Cognitive training benefits the trained skill

J Gerontol: Med Sci. 2004. 59a(9)
Am J Geriatr Psychiatry, March 17, 2009

- ACTIVE Study
  - 5-year follow up
  - 2800 community dwelling persons
    - Mean age 73.6
  - Cognitive training: memory, problem solving, processing speed, no-contact control
  - Improvement in cognition on the targeted cognitive ability over 5 yrs
  - Problem solving training resulted in less functional decline in IADLs

JAMA, December 20, 2006, Vol 296

Medications

- Prescription medications
  - Cholinesterase inhibitors
    - Trials have not supported the use of cholinesterase in preventing the conversion from mild cognitive impairment to dementia
      - Increased treatment-associated adverse events
  - Memantine
    - Lack of efficacy in mild Alzheimer's disease

Arch. Neurol. 2011;(68):991–998

Cochrane Database Syst Rev, 2012. Cholinesterase Inhibitors for Mild Cognitive Impairment

Medications

- Prescription medications
  - Hormone therapy
    - Estrogen has not shown to be helpful in preserving cognitive function in non-demented postmenopausal women
      - May have adverse effect on cognition (WHIMS)
  - NSAIDs
    - Not recommended, may increase risk of cerebrovascular and cardiovascular events
  - Statins
    - Not recommended, case reports of cognitive dysfunction

JAMA. 2004;291(24):2959.

Medications

- Supplements
  - Gingko biloba
    - RDPCT no evidence of slowing cognitive decline over 6 years, >3000 community dwelling older adults
  - Vitamin E
    - No evidence of benefit in patients who are cognitively intact
    - May increase all-cause mortality
    - May slow rate of functional decline in patients with established mild/moderate AD
      - No evidence of cognitive benefit

JAMA. 2009;302(24):2663 Arch Neurol. 2006;63(11):1545
JAMA. 2014 Jan;311(1):33-44.
Ann Intern Med. 2005 Jan 4;142(1):37-46

Medications

- Supplements continued
  - Omega 3 Fatty Acids
    - Reduced risk of cognitive decline, dementia, and WM hyperintensities
      - Framingham study showed 47% reduced risk of dementia in group that had highest plasma DHA levels, 9 year follow up
    - Randomized trials have not shown benefit to cognitive function
      - Lack power and duration to test whether there is reduction to dementia risk
    - 1g EPA/DHA may be reasonable given positive effect on cardiovascular risk factors (though 1-2 servings of fish per week is better!)

Summary

- The brain changes with age
- Thinking and memory changes as well
- There are ways to promote healthy brain aging
  - Exercise
  - Stay social
  - Mediterranean diet
  - Cognitive exercises

The End

Email Me

mansoord@ohsu.edu

Quick Radic:

Efficient and Effective Assessment for Radiating Upper Extremity Pain

OHSU 26th Annual Internal Medicine Review
190412

Erik Ensrud, MD
Associate Professor, Orthopaedics and Rehabilitation, OHSU
Board Certified in PM&R/EMG/Neurology/Neuromuscular Disease

What is the percentage of your patients are complaining of radiating arm or leg pain?

A. < 5%

B. 5-10%

C. 10-15%

D. 15-20%

E. > 20%

Ms.K, a 38 yo new pt, c/o 2 months right arm pain that shoots down arm just past elbow. You decide to…

A. Order a cervical MRI

B. Order an EMG

C. Examine 8 muscles for strength

D. Examine 6 muscles, one neck test, and 3 shoulder tests

E. Examine 4 muscles, 2 MSK tests, and 3 sensory points…and do this in < 60 sec

PAIN THAT TRAVELS ALONG A LIMB

Radiating (vs radicular) pain is a very common clinical complaint

Often assumed to be radicular

radicular pain-pain "radiated along a dermatome of a nerve due to inflammation or irriation of a nerve root"

But radiating pain is often *not* due to nerve irritation-*muddles* the workup

So sometimes radiating pain can be MSK

But many DO have radicular pain from pinching of nerve roots…how to effectively find that ?

Let's start with what we are looking at…

Let's back up…what Do Normal Peripheral Nerves Do?

3 Functions

1. Carry a signal to muscle to contract
2. Carry normal sensation such as light touch for skin
3. *Carry pain messages from non-nerve tissues (skin, bone, joints, soft tissue). *This message does not mean that the nerve is injured or abnormal.*

Such as, a fire alarm going off may mean the fire alarm is injured/malfunctioning (injured nerve), or…
that the fire alarm is working as designed to carry a message that there is a fire-in this case the fire alarm/NERVE is functioning normally.

Ordering an MRI as First Step

- BENEFITS
  - Time saver-few clicks…"Smart" Set
  - Likely to be abnormal-confirmation bias
  - Pts are always worried about their spine, want to know
  - Very sensitive test
  - Picture for the Instagram Age
- Drawbacks
  - High likelihood of normal abnormalities
  - Often requires pre-auth, denials
  - Much explanation needed in f/u about disc bulges, foraminal stenosis on wrong side
  - Often low specificity test

Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990;72(3):403–8.
Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med 1994;331(2):69–73.

Exam?? We're going somewhere, but it's foggy and old-fashioned….

Amish community outside of Champaign-Urbana, IL

Is the exam relevant today?

Sun setting on that way back when windmill thing…

MOTOR EXAMINATION

- Advantages
  - FEE-Fast, Easy, Effective in clinic
  - QUICK-much faster than even rapid CT
  - Can provide valuable info regarding the longest tracks throughout the central and peripheral nervous system
  - Pattern recognition allows for rapid diagnosis
- Disadvantages
  - Relies on pt effort/level of alertness/cooperation
  - Relies on examiner's interpretation of muscle force
  - Difficult to learn this on the web or in a book-it's a learned motor skill, like riding a bike

Basic Principles of Muscle Force Testing 1

- Each muscle crosses a joint and causes changes in that joint ROM with contraction
- Try to STABILIZE the joint the muscle crosses whenever possible, to help isolate the muscle action

Basic Principles of Muscle Force Testing 2

- Use your similar-sized muscles only in hand muscles
- You will use your perception of the force you deliver and your experience of what is "normal"-this is a learned motor skill and takes time to learn-*try to do a focused exam on pts with known diagnoses so that you know what to expect*
- In motor testing, the EXAMINER has the subjective sensation being judged-c/w sensory where the PATIENT has the subjective sensation
- In non-hand muscles, use your additional muscles/body weight as needed-this is not a force competition (i.e., I am stronger and therefore the pt is "weak" or vice-versa)

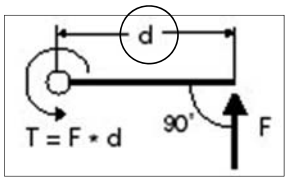
Basic Principles of Muscle Force Testing 3

- Muscle Strength testing =
  - = Force (M x A)
    - Measured in Pounds/Kilograms/Newtons
    - Not time dependent
- Work =
  - = Force x Distance
  - Units are joules

- Power =
  - = Work/time
  - Units are units of energy divided by time,
  - i.e watt = one joule/second

TORQUE !

- The tendency of a force to rotate an object about an axis (aka joint in MST)
  - Physics = Torque
  - Mechanical Engineering = Moment

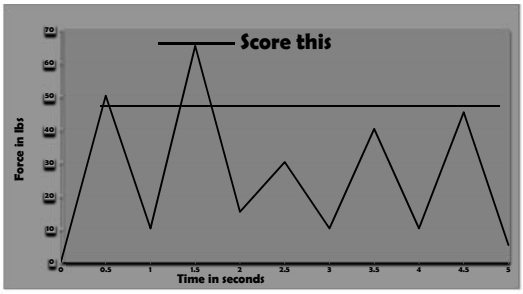


Maximize d !!

Basic Principles of Muscle Force Testing 4

- The score assigned to the muscle is the maximum force generated at any point in time during the testing of that muscle
- Rapid decreases in force do not represent weakness; rather, almost without exception they represent variability in lower motor neuron drive (exception-severe myasthenia)
- * Do not report the average when intermittent activation occurs-report the **PEAK** force

Score Peak force



Another look at peak strength testing

Intermittent Activation (IA): The Great Strength Confounder

"The Chicken Dance"

- Three Reasons for IA
  - Pain in joint crossed-contraction of muscle compresses joint
  - Poor proprioception/ position sense -cannot sense the contraction of muscle/joint position well
  - "Enhancement" of weakness (somatic vs. malingering)

Back to MsK…consensus is examine first…

What nerve roots might be affected with radiating pain down an arm? C6>C7>C5>C8

Surgical detail	Primaries	Revisions
No. of procedures	1,305	115
Levels	2,811	198
Average levels/procedure	2.2	1.7
Levels affected		
C2	20 (1.5)	0
C3	96 (7.4)	8 (7.0)
C4	285 (22)	31 (27)
C5	493 (38)	35 (30)
C6	855 (66)	31 (27)
C7	803 (62)	49 (43)
C8	195 (15)	33 (29)
T1	64 (4.9)	11 (9.6)

We know that C6 is the most common cervical radiculopathy, what is the best muscle to check strength for C6?

A. Deltoid

B. Biceps

C. Pronator teres

D. Triceps

E. Wrist Extension

Pronator Teres-most sensitive muscle for C6

* the most distal C6-innervated muscle

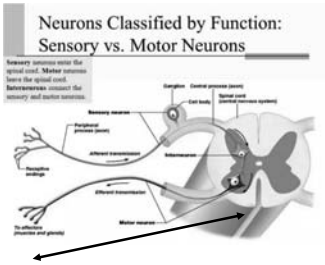
Assessment of Forearm Pronation Strength in C6 and C7 Radiculopathies

James Rainville, MD,*† Damon J. Soto, MD,† Cristie Jouve, MD,*† and Louis Jenis, MD*‡§

Results. In C6 radiculopathy subjects, forearm pronation weakness was present in 72%, was twice as common as wrist extension weakness, was present in all case where elbow flexion or wrist extension weakness was noted, and was found in all but 2 subjects where elbow extension weakness was present. In C7 radiculopathy subjects, forearm pronation weakness accompanies elbow extension weakness in 23% of subjects and was the only weakness in 10% of subjects. Manual muscle testing demonstrated adequate interrater reliability.

Conclusions. Forearm pronation weakness is the most frequent motor finding in C6 radiculopathies and may be noted is some cases of C7 nerve root compression.

Why is that?
Unique nature of structure of peripheral neurons-the LONGEST cells in the body, very length-dependent transport along the length of the very long cell

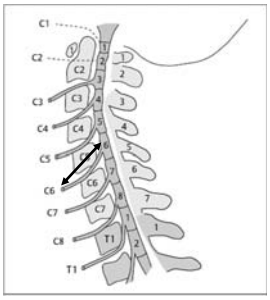


In an arm, 2+ feet long!

Nerve root compression is similar to a dam at a **creek spring…where does the creekbed start to run dry? Near the spring or downstream?**
Pronator teres is the most "downstream" C6 muscle

Why was this missed? What about ASIA (American Spinal Injury Association) scales? What about wrist extension?

- ASIA motor levels are based on SPINAL CORD levels
- Motor neurons in the spinal cord are always superior/above their nerve root exit from the spinal cord
- Because of this, spinal cord and nerve root levels do not correlate well

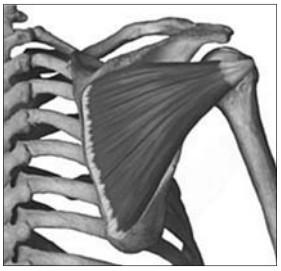


4 Muscle, Side to Side Comparison, C5-8 Screen

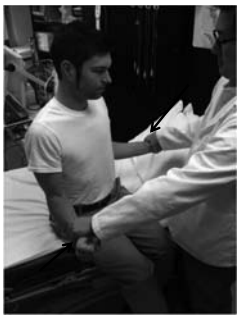
- Infraspinatus C5
- Pronator teres C6
- Extensor Digitorum Communis (EDC) C7
- Extensor Indicis Proprius (EIP) C8

Infraspinatus force testing-C5

side to side immediate comparison (also upper motor neuron advantages)



Extends and laterally rotates the humerus



Pronator Teres-most sensitive muscle for C6

* the most distal C6-innervated muscle

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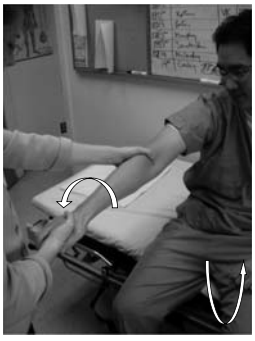
Pronator teres-C6



- Shake pts hand, ask them to keep the thumb DOWN
- Pts elbow must be fully extended (if flexed test pronator quadratus)
- Weak in ~2/3 of C6 radics
- check side-to-side
- Bend your trunk sideways prn for additional force

EDC (Extensor digitorum communis) highly C7

- Have pt grasp knees with all fingers, then lift up the 2 middle fingers
- "flip the bird"
- Minimal force muscle, like all finger extensors
- Don't push too hard too fast-marshmallow analogy
- Check force side-to-side

Extensor indicis propius (EIP) radial nerve, highly C8

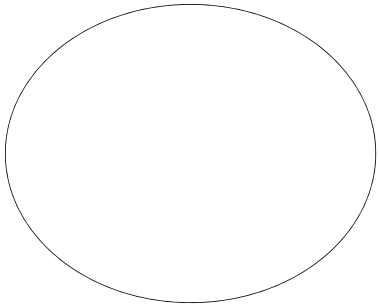
- Have pt grasp knees with all fingers, then lift up the 2 index fingers
- Slight force muscle, like all finger extensors-finger flexors much stronger (cause of trigger fingers)
- Check force side-to-side
- Great advantage of not being involved in ulnar neuropathy or CTS

SENSORY EXAM

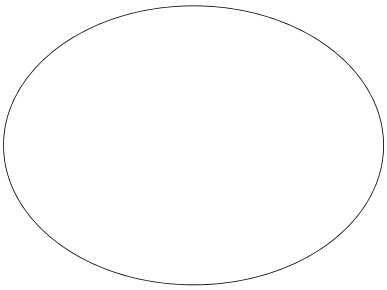
- "CAN YOU FEEL IT" IS A…
  - A. Good question to ask during the usual sensory exam
  - B. 1980 epic hit single/video by The Jacksons
  - C. Poor question to ask a pt with an acute spinal cord injury
  - D. Album by the innovative 1980's Australian band, Hunters and Collectors (best known for their single, "Throw Your Arms Around Me")

CAN YOU FEEL IT

Which circle is darker gray?



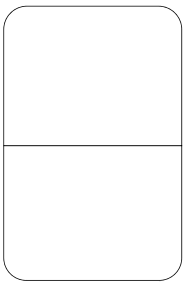
PAUSE



Which of those 2 previous ovals was darker- the 1st or 2nd?

A. First
B. Second

DST-double simultaneous testing



DST-double simultaneous testing

- Use to test
  - Distal to proximal gradients for length-dependent neuropathy.
    Light touch is best-subserved by both systems
  - Side-to-side distal dermatomes for radiculopathy
  - Different peripheral nerve distributions for focal neuropathies

Side to side distal aspect of dermatomes for radiculopathy

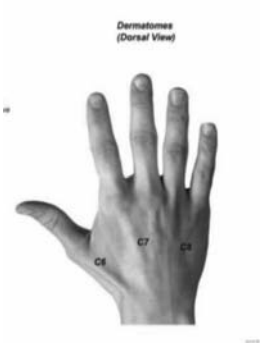
Simultaneously touch
Back of Left and Right hand

Thumb C6

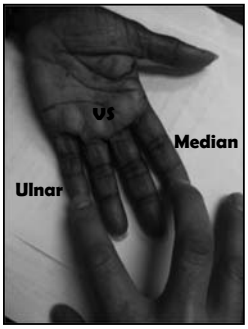
Middle Finger C7

Pinky C8

10 sec



Different peripheral nerve distributions for focal neuropathies



Back to MsK…cervical radic muscle screen negative…

What else might be affected with radiating pain down an arm?

MSK Mimic-definition

A musculoskeletal condition that presents with pain or discomfort suggestive of a nerve injury/neuropathic etiology

Reasons to care about MSK Mimics

Common causes of limb pain

Frequent reason for clinic referral

Pts may have radiculopathy AND mimics

Your extremity skeleton and spinal nerve roots don't coordinate their pain-like your 2 kids crying at the same time about different things

"Pain in limb-? radiculopathy, ? CTS"

Treatable conditions

Musculoskeletal Exam Tests: Advantages

FAST/EASY/EFFECTIVE

Ability to diagnose quickly at bedside or exam room with appropriate physical exam

Timesavers for the Provider…keep up your clinic flow

Fewer unnecessary MRIs ordered with time-consuming follow-up

Musculoskeletal Exam Tests: Pearls

Check bilateral limbs for side-to-side comparison: non-involved side first when possible

Ask, "Is that the same pain you have been experiencing?"

* Patients can have more than one condition-i.e. radiculopathy *and* rotator cuff tendinitis

Musculoskeletal Exam Tests Pearls: Wince sign

Look for the "Wince" sign for positive test

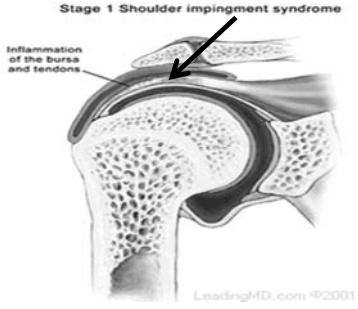
- **Eye blink/face grimace**
- **Not just mild discomfort**

When doing an MSK test, Watch their eyes

2 High-Yield MSK Mimic Tests for Radiating/? Radic Exam

- Hawkins Sign
- Lateral epicondyle tenderness

Supraspinatus/Rotator Cuff Tendonitis



Supraspinatus tendonitis mimics

C3-7 radiculopathy*

Supraspinatus tendonitis Symptoms/risk factors

Pain with arm movement, esp. overhead

*Difficulty sleeping when lying on affected side

Pain may radiate up towards neck and down arm, even beyond elbow

Repetitive movements-esp. overhead, acromion anatomy (hooked)

Especially in people with underlying neurologic disease, due to periscapular muscle imbalance leading to instability of glenohumeral joint

Supraspinatus Tendonitis: Hawkins Shoulder Test most sensitive at 92%

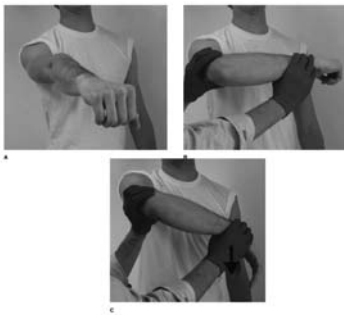
Humerus flexed 90 deg

Elbow flexed 90 deg

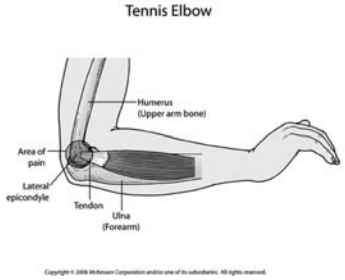
Examiner's hand stabilizes pt's shoulder

Examiner pulls down on pt's forearm WITH RAPID JERK to internally rotate humerus…forceful enough to knock over a full pint glass on a tabletop

Head of humerus pinches tendon under acromion → PAIN when inflamed



Lateral epicondylitis



Lateral epicondylitis mimics

Lower cervical radiculopathy-pain can radiate distally along forearm/ulna

Ulnar neuropathy*-pain around elbow, radiates from elbow

**Ulnar nerve will go into pinky and ring finger…usually different from radiculopathy

Lateral epicondylitis-exam test

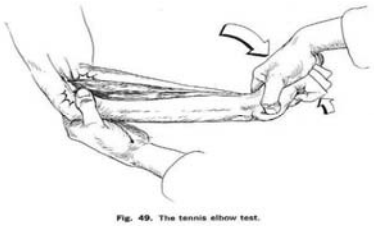


Fig. 49. The tennis elbow test.

- Palpate 0.5-1cm distal to the epicondyle (max . tenderness to palpation)

Practice with another participant

4 Muscle, Side to Side Comparison, C5-8 Screen

- Infraspinatus C5
- Pronator teres C6
- Extensor Digitorum Communis (EDC) C7
- Extensor Indicis Proprius (EIP) C8

L/R Light Touch-C6/7/8

Hawkins and Lateral epicondyle Tests

Back to MsK…cervical radic muscle screen negative, light touch C6/7/8 L/R equal…

Markedly positive R Hawkins Test, negative lateral epicondyle TTP

Now you have options…

1. Home rotator cuff exercises
2. PT Referral
3. Subacromial steroid injection
4. Some combination of the above

RTC 2 months…MUCH better ☺

Review-Quick Radic, Upper Extremity

- 4 muscle force screen 30 sec
- L/R light touch comparison 10 sec
- Hawkins and Lateral Epicondyle MSK Tests 20 sec

When fishing for radiating upper extremity pain…

Cervical Spine MRI

Quick Radic Exam

THE END

Happy to discuss a patient or see your referral
ensrud@ohsu.edu, or text page me on OHSU system

Larry Kanfer Photography
Champaign-Urbana, IL

Rational Use of Antiplatelet Agents

Tom DeLoughery, MD MACP FAWM

Oregon Health and Sciences University Knight Cancer Institute at Oregon Health & Science University

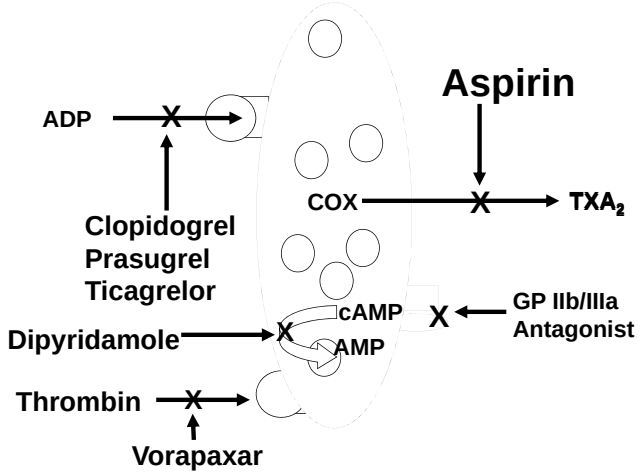
DISCLOSURE

Relevant Financial Relationship(s)

Speaker Bureau – None

What I am Talking About

1. **Current indications for antiplatelet agents**
2. **Review the agents**
3. **Combined therapy**

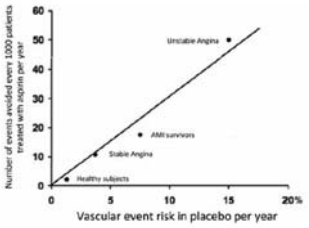


Aspirin

- Blocks production of thromboxane A_2
- Effects last life of the platelet
  - Drug has only short half-life
- First line agent for any arterial ischemic disease
- Dose
  - Acute > 162.5 mg
  - Chronic 81 mg/day

Aspirin Therapy

- Greater benefit with greater risk of event



Aspirin: Secondary Prevention

Category of trial	No of trials with data	No (%) of vascular events: Allocated antiplatelet	Adjusted control	Observed-expected	Variance	Odds ratio (CI) Antiplatelet:control	% Odds reduction (SE)
Previous myocardial infarction	12	1345/9984 (13.5)	1708/10 022 (17.0)	-159.8	567.6		25 (4)
Acute myocardial infarction	15	1007/9658 (10.4)	1370/9644 (14.2)	-181.5	519.2		30 (4)
Previous stroke/transient ischaemic attack	21	2045/11 493 (17.8)	2464/11 527 (21.4)	-152.1	625.8		22 (4)
Acute stroke	7	1670/20 418 (8.2)	1858/20 403 (9.1)	-94.6	795.3		11 (3)
Other high risk	140	1638/20 359 (8.0)	2102/20 543 (10.2)	-222.3	737.0		26 (3)
Subtotal: all except acute stroke	188	6035/51 494 (11.7)	7644/51 736 (14.8)	-715.7	2449.6		25 (2)
All trials	**195**	**7705/71 912 (10.7)**	**9502/72 139 (13.2)**	**-810.3**	**3244.9**		**22 (2)**

0 0.5 1.0 1.5 2.0
Antiplatelet better Antiplatelet worse

Heterogeneity of odds reductions between:
5 categories of trial: χ^2=21.4, df=4; P=0.0003
Acute stroke *v* other: χ^2=18.0, df=1; P=0.00002
Treatment effect P<0.0001

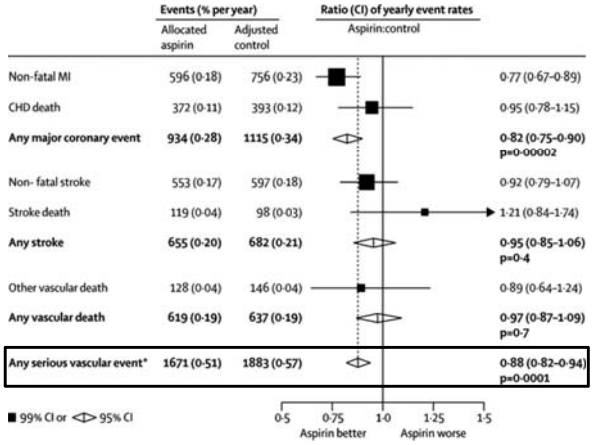
BMJ. 2002 Jan 12;324(7329):71-86

Aspirin: 2nd Prevention

- In patients with event the use of aspirin is associated with 22% reduction of future events and 15% reduction in death
- Aspirin is recommended for anyone with a history of a vascular event

ASA: 1 Prevention
The Early Days

- BDS: 6% reduction in MI (NS)
- PHS: 44% reduction first MI
- TPT: 20% reduction in MI
- HOT: 36% reduction in MI
- PPP: 29% reduction in MI
- WHS: 9% reduction in MI (NS)



Lancet 373:1849, 2009

1 Prevention (< 2000)

- 12% reduction in serious vascular events
  - 0.51%/yr vs 0.57%/yr
- 20% reduction in MI
  - 0.18%/yr vs 0.23%/yr
- No difference in death or stroke
- But trials done before widespread statin use

The New Era

- ASCEND
- ARRIVE
- ASPIRE

ASPREE

- Healthy >70 yo
- N = 19,114

	ASA	Control	Sig
Events	1.07	1.13	NS
Bleeds	0.86	0.62	Sig
Death	1.27	1.11	Sig
Cancer	0.31	0.23	Sig

NEJM 379: 1509, 1519 2018

ARRIVE

- N = 12,546 with CV risk factor

	ASA	Control	RR
Events	4.29	4.48	NS
GI Bleeds	0.97	0.46	2.11
Death	2.55	2.57	NS

Lancet: 392:21036, 2018

ASCEND

- N = 15,470 with DM

	ASA	Control	RR
Events	8.5	9.6	0.88
Bleeds	4.1	3.2	1.29
Death	9.7	10.2	0.94 (NS)

NEJM 379:1529, 2018

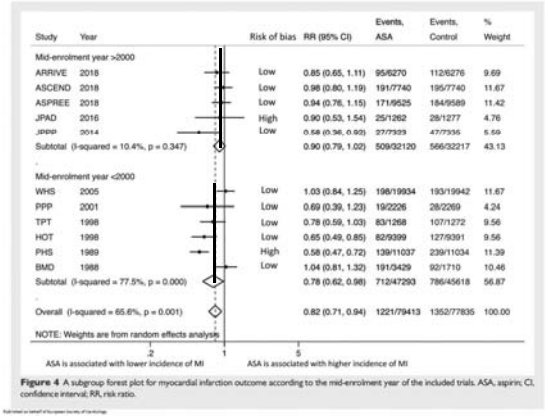


Figure 4 A subgroup forest plot for myocardial infarction outcome according to the mid-enrolment year of the included trials. ASA, aspirin; CI, confidence interval; RR, risk ratio.

New Trials: Summary

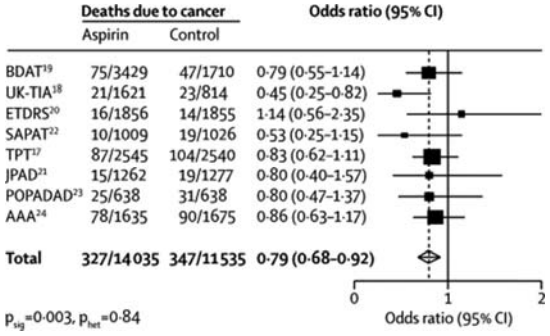
- Reduction CV events: 0.89
  - Absolute: 0.38%
- Increase in Bleeding: 1.43
  - Absolute: 0.47%
- JAMA 2019;321(3):277-287

Now What?

- Risk in primary prevention of aspirin greater than benefit
- Statins and BP control paramount

But….

- Increasing evidence long term use of aspirin prevents cancer
- Study of 8 long term aspirin trials for CV disease with analysis of cancer endpoints
- N = 25570



Lancet. 2011 Jan 1;377(9759):31-41

ASA for Cancer Prevention

- Clearest for colorectal cancer
  - Consider in patients with polyps or family history
- Barrett's
  - Positive RCT
- Smokers- Lung?
- Needs to be in risk benefit discussion of aspirin

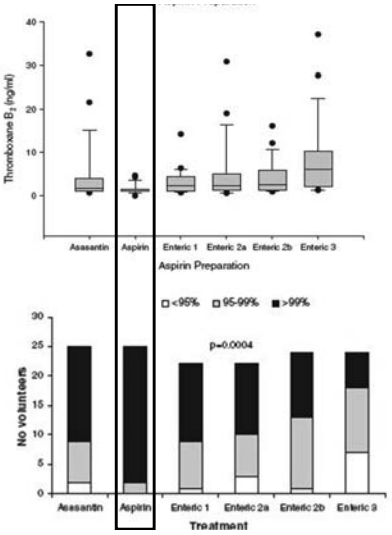
ASA: Bottom Line

- Secondary Prevention- YES!
- Primary – No unless
  - Cancer risk factors
  - Evidence of atherosclerosis

Aspirin: Using it Right!

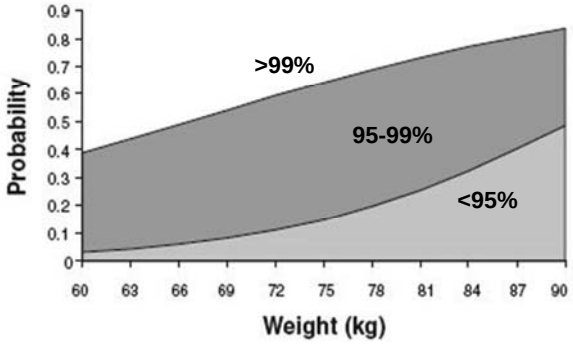
- No benefit with higher doses > 81mg
  - More bleeding
- Formulation of pill may matter

Aspirin:
Avoid coated or enteric products

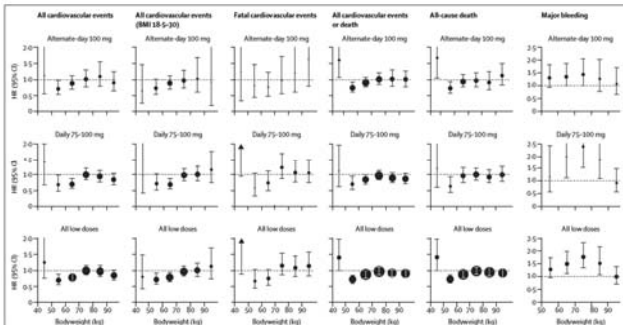


Stroke. 2006 Aug;3:2153-8

Especially in Heavy Patients



Stroke. 2006 Aug;3:2153-8



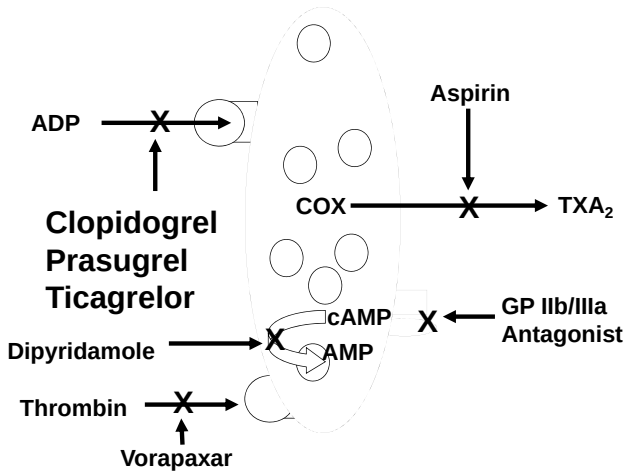
Lancet. 2018 Aug 4;392(10145):387-399

Enteric and Coated ASA

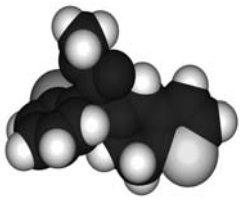
- May play a role in resistance and ASA failures with 81 mg ASA
- Very difficult to find uncoated aspirin
  - Chewable good option
  - More data to come out about weight

The Search for a Better Aspirin

- Many patients still have events on aspirin
  - RR of 22% implies ~80% will have events
- Can we do better?



Clopidogrel



- Permanently blocks platelet ADP receptor
- Early trials showed equivalence to aspirin
- Most frequent use involves combination therapy with aspirin

Clopidogrel in ACS

- Start immediately
  - 300mg bolus then 75mg po
  - ST-Elevation ACS 14 days
    - Consider one year
  - Non-ST Elevation ACS one year

Coronary Stents

- Stent thrombosis is a devastating event
  - 50% death rate
- Prevention
  - Warfarin is not that effective!
  - Antiplatelet agents key

Stents: Antiplatelet Agents

- Bare metal
  - ASA + Clopidogrel for 4 weeks then ASA
- Drug eluting
  - Long term combined therapy
    - 1st generation – 1 year
    - New stents (-'limus) – 6 months

Stents

- Increasing trials and registry data 6 months may suffice
  - Less bleeding
  - Less costs
- Recent trial of 12 vs 30 months

Stents 12 vs 30 months

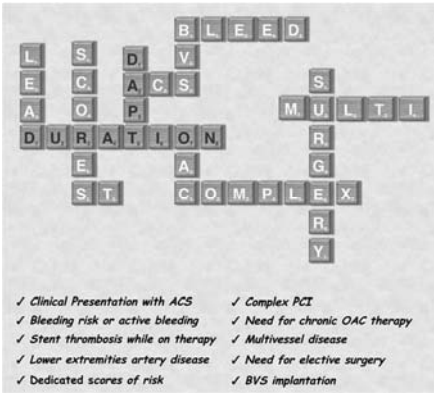
- N = 9961 patients
- 30 months has
  - Less stent thrombosis (0.4 vs 1.4%)
  - Less arterial thrombosis (4.3 vs 5.9%)
  - More bleeding (2.5 vs 1.6%)
  - More death (2.0 vs 1.5%)
- N Engl J Med 2014; 371:2155-2166

Meta-Analysis

- 10 trials – 31,666 patients
- 6 months vs 12 months
  - Equal death
  - Equal cardiac
  - Less bleeding
- ¼ trials of > 12 month therapy with better primary outcome
- Shorter (≤6 months) with less death
- Lancet 2015

Bottom Line

- Duration remains contentious
- Consistent signal of increase noncardiac death
- Mandatory period
  - Depends on stent type
    - 3-6 months for 'limus stents
- Possible beneficial period
  - Longer
    - MI, high risk stents, low risk bleeding



Cardiovasc Diagn Ther. 2018 Oct;8(5):630-646.

Aspirin plus Clopidogrel

- Other disease states?
  - History of stroke (worse)
  - Atrial fibrillation
  - Chronic atherosclerosis
  - Primary prevention
- All trials essentially negative

Acute Stroke

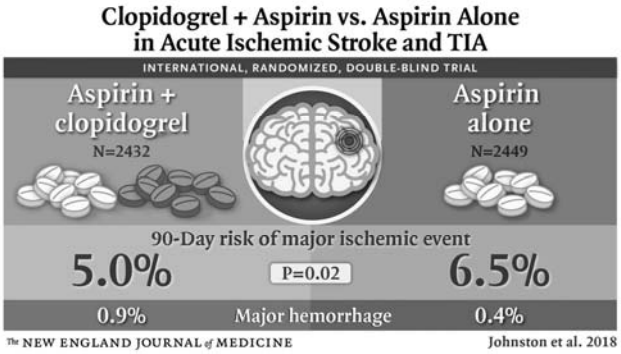
- Evidence that short term combination therapy may be helpful in acute stroke

POINT

- **N = 4,881 with "high risk TIA/minor stroke"**

	DAPT	ASA	RR
Events	5.0	6.5	0.75
Bleeds	0.9	0.4	2.32
Stroke	4.6	6.3	0.72

Most events prevented in first week
NEJM 379:215, 2018



DAPT after Stroke/TIA

- **Start within 24 hours**
  - **Stroke reduced absolute risk reduction 1.9%**
  - **Increase bleeds 0.2%**
  - **Most benefit first 10 days and none after 21 days**

Clopidogrel: Bottom Line

- **Use in aspirin allergic patients**
- **Combination therapy for stents or ACS**
- **Acute stroke/TIA**

Prasugrel

- **New thienopyridine**
  - **Still requires activation**
  - **Inhibits platelets faster and more reliable than clopidogrel**
- **PCI: better than clopidogrel but one bleeding death for every 7 MI prevented**

Ticagrelor

- **"Reversible" P_2Y_{12} receptor inhibitor**
  - **Still takes 5 days to wear off!!!**
- **Non-thienopyridine**
- **Very effective in ACS**
  - **Reduce deaths**
  - **No increase in major bleeding**

Ticagrelor: Bottom Line

- 180mg load then 90mg bid
- More effective than clopidogrel in acute coronary syndromes
- Cannot use > 100 mg of aspirin
- May be effective in long term therapy of high risk patients

Aspirin/ER Dipyridamole

- Effective agent for stroke prevention
- CANNOT use generic DP plus aspirin
  - Shown to be worthless
- Indications:
  - Patients s/p mild stroke or TIA
  - NOT indicated for cardiac disease
- Start with one at pm and go to bid

Bottom Line

- Aspirin is Good!
  - Keystone of acute therapy and secondary prevention
- Combination therapy
  - ACS
  - Stents
  - Acute strokes (?)
- Prasugrel and vorapaxar place needs to be defined
- Ticagrelor promising

Aspirin for Venous Disease

- Classically thought to be only for arterial disease
- But platelets do play a role in venous disease

Aspirin for DVT Prophylaxis

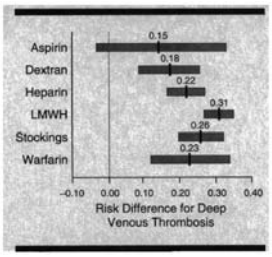
- Broad appeal
  - Cheap
  - Simple
- Wide spread use
- What is the data?

Early Trials

- Inconsistent data 1960-90
- Analysis of multiple trials and antiplatelet agents found ~ 30% risk reduction
  - Variable dose
  - Variable gender effect

Early Trials

- Meta-Analysis of aspirin only trials with good design showed no benefit
- JAMA 271:1780 1994



PEP Trial

- N = 13,356
- Aspirin 160mg vs placebo
- Other form of prophylaxis allowed
- Controversial changes of definition of major events during trial
- Lancet 355:1295, 2000

PEP Trial

- Hip fracture
  - 29% risk reduction
  - Increased MI
  - Benefit seen after first week
- Hip/knee arthroplasty
  - No benefit
- No large trials since
  - POISE-2 with no major benefit

Aspirin and Bleeding

- Aspirin is associated with a 2.2/100 excess rate of hematoma and infection
- Overall hematoma rates
  - Placebo: 5.6%
  - Aspirin: 7.8%
  - UFH: 6.0-6.2%
  - LMWH: 5.0-7.1%
- Arch Surg 141:790, BMJ: 1994; 308 : 235

One Potential Benefit

- PEP only showed benefit after a week
- Trial of LMWH for 10 days and then LMWH vs aspirin for the next 28 no difference in thrombosis
- Annals 158:800, 2013

Rivaroxaban vs Aspirin

- RCT of 3424 patients
- All got 5 days 10mg rivaroxaban
  - Then randomized to 81 mg ASA or continue rivaroxaban
  - Hip 30 days and knee 9 days
- N Engl J Med 2018; 378:699-707

Results

- Thrombosis
  - Riv: 0.70% Asa: 0.60%
- Bleeding
  - Riv: 0.29% Asa: 0.47%
- Note: patients with hx of DVT excluded

Aspirin: Bottom Line

- Inconsistent data
- No consistent dose
  - 160 – 3900mg/day
- Does raise risk of bleeding
- Low risk patients: mechanical effective
- Average: Aspirin an option after 7-10 of effective prophylaxis
- High risk patients: more effective options

Aspirin

- Long controversy about role in secondary prevention of venous thrombosis
- HERS – 50% decrease DVT
- Prospective 1° prevention trial in FVL negative
  - Used ineffective dose of aspirin

Aspirin

- Two trials one positive and one negative
  - N Engl J Med 2012;366:1959-1967
  - N Engl J Med 2012; 367:1979-1987
- Meta-analysis suggestive of effect

Aspirin

Event	Aspirin	Placebo	HR
RVTE	13%	19%	0.68 (0.51-.90)
Vascular Events	16%	22%	0.66 (0.51-0.86)
Major Bleeding	3%	2%	1.47 (0.70-3.1)

N Engl J Med 2012; 367:1979-1987

Rivaroxaban: Chronic Venous Thrombosis

- N = 3365 with VTE (some provoked)
  - 50% with PE
  - 6-12 months of therapy
- RCT
  - Rivaroxaban 20 mg daily
  - Rivaroxaban 10mg daily
  - Aspirin 100mg daily
- N Engl J Med 2017; 376:1211-1222

Results

	Rivaroxaban 20mg (1107)	Rivaroxaban 10mg (1127)	Aspirin 100mg (1131)
Recurrent VTE	17 (1.5%)	13 (1.2%)	50 (4.4%)
Any Bleeding	196 (17.8%)	160 (14.2%)	143 (12.8%)
Major Bleeding	6 (0.5%)	5 (0.4%)	3 (0.3%)

Aspirin in VTE

- No role for aspirin in secondary prevention of VTE
- DOACs work <u>better</u> and are just as safe!

Aspirin and Afib

- Aspirin often given to afib patients because it is perceived to be “safer” and effective
- But is it???

BAFTA

- N = 973 with afib
- All over 75 year of age (mean 81.5)
- RCT
  - Warfarin 2-3 vs aspirin 81mg/day
  - f/u 2.7 years
- Lancet 2007; 370:493-503, 460-461

BAFTA

End point	Warfarin	Aspirin	Hazard ratio (95% CI)
Stroke (%/yr)	1.6	3.4	0.46 (0.26-0.79)
Major extracranial hemorrhage (%/yr)	1.4	1.6	0.87 (0.43–1.73)
All major hemorrhages (%/yr)	1.9	2.2	0.96 (0.53–1.75)

Mant JW et al. *Lancet* 2007; 370:493-503, 460-461.

Hazard Ratios For Bleeding Compared To Aspirin

Drug/combination	Adjusted hazard ratio	95% CI
Clopidogrel	1.33	1.11–1.59
VKA	1.23	0.94–1.61
Aspirin/clopidogrel	1.47	1.28–1.69
Aspirin/VKA	1.84	1.51–2.23
VKA/clopidogrel	3.52	2.42–5.11
VKA/clopidogrel/aspirin	4.05	3.08-5.33

Sørensen R et al. *Lancet* 2009; 374:1967-1974.

Aspirin vs Apixaban

- RCT
  - Aspirin 81-324mg
  - Apixaban 5mg bid
- More effective than aspirin
  - RR 0.45 (0.32-0.62)
- Same risk of bleeding
  - RR 1.13 (0.74-2.05)
  - Intracranial hemorrhage 0.85 (0.38-1.90)

Aspirin vs Warfarin

- 52% reduction in ischemic stroke with warfarin
  - History of stroke ARR = 6%/yr
  - No history of stoke ARR = 1.2%/yr
  - Low risk of stroke ARR = 0.4%/yr

Aspirin and Stroke Severity

- Aspirin does not reduce risk of disabling stroke
  - 22-->13% (NS)
- Warfarin does reduce fatal stroke
  - 0.5-->0.2 events/yr

AHA Guidelines 2014

- No studies, with the exception of the SPAF (Stroke Prevention in Atrial Fibrillation)-1 trial, show benefit for aspirin alone in preventing stroke
- Ineffective in preventing strokes in those >75 years of age
- Did not prevent severe strokes
- Has not been studied in a population at low risk of AF
- Not even mentioned in 2019 update!

Aspirin: Bottom Line

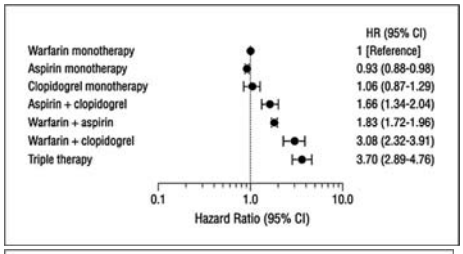
- Limited to no effectiveness
- Not effective in older patients
- Not effective in preventing disabling strokes
- Not the safer choice
- Not recommended!

Combining Anticoagulation

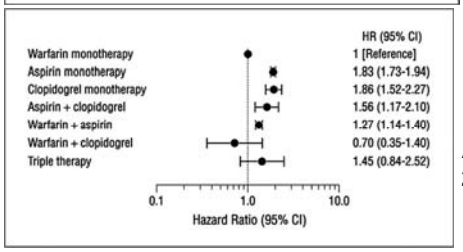
- Aspirin + Clopidogrel
- Aspirin + Warfarin
- Aspirin + DOAC
- “Triple Therapy”

Why Worry

- Increasing intensity of anticoagulation increases the risk of bleeding but also thrombosis



Bleeding Risk



Stroke Risk

Arch Intern Med. 2010;170:1433-1441

Aspirin + Clopidogrel

- Effective in
  - Acute coronary syndromes
  - Stents
- Not effective
  - Late secondary and any primary prevention
  - Atrial fibrillation
- Harmful
  - Strokes (except acute)

Warfarin and Aspirin: Valves

- Clear data that adding of aspirin to warfarin in patients with mechanical valves
  - Decreases embolic risk
  - Decreases mortality
  - Increases major bleeding by 20%

Warfarin and Aspirin: Atrial Fibrillation

- Afib and CAD co-exists in many patients
- Trial data
  - No benefit in stroke prevention
  - No benefit in MI prevention
  - Increase risk of major bleeding

Should Warfarin ever be Added to Aspirin?

- Increases risk of bleeding significantly
- Good Idea
  - Mechanical Valve
  - Stents
  - (ACS)
- Bad idea
  - Primary prevention
  - Long term secondary prevention
  - Peripheral vascular disease
- Always think before combing ASA and warfarin

DOAC + Aspirin

- Increased risk of bleeding
- Unclear in patients on DOAC with CVD if adding aspirin will help
- May be benefit of DOAC + ASA in high risk patients
  - Recent events or ongoing symptoms

Surgery

- Aspirin
  - Stop 5 days before
- Clopidogrel, Prasugrel
  - Stop 5-7 days before
- Ticagrelor
  - 5 days before

Drug Eluting Stents

- Combination therapy for at least 3-6 months
- No elective surgery!
- If need to stop one agent, stop aspirin
- Need to consider if patient can take 3-6 months of clopidogrel before using drug eluting stent

Summary

- Primary prevention: no!
- Secondary prevention: YES!
- ASA + clopidogrel: Stents and strokes
- Maybe DVT prevention
- Not afib!