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Sunday, August 4, 2019

G Controversies in Cancer Screening 2019: Colon, Breast, Lung, and Prostate 
Judith M.E. Walsh, MD, MPH

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Monday, August 5, 2019

RxG Management of Lipid Disorders: Integrating the New Guidelines 
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RxG Common Dermatologic Problems: What the Primary Care Physician Needs to Know 
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RxG Skin Diseases in the Aging Patient 
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RxG Depression in Primary Care: Mourning or Melancholia? 
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WORKSHOPS
A: Dermatologic Procedures in Primary Care 
Toby A. Maurer, MD

B: Advances in Women’s Health: A Critical Review of the Year’s Most Important Papers 
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| C: Somatic Symptom Disorder and Related Disorders: Clinical Pearls in Assessment and Treatment | Descartes Li, MD |
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### Thursday, August 8, 2019

| RxG | Contraceptive Update: New Methods, New Guidelines | Michael S. Policar, MD, MPH |
| RxG | What’s New in Management of Menopause and Perimenopausal Symptoms? | Judith M.E. Walsh, MD, MPH |
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| RxG | Screening and Diagnosing Dementia in Primary Care | Leah S Karliner, MD, MAS |
| RxG | Managing Sleep and Its Disorders: Beyond Sleep Hygiene | Descartes Li, MD |
Division of General Internal Medicine
University of California, San Francisco School of Medicine
presents

Essentials of Primary Care
A core Curriculum for Ambulatory Practice

August 4-9, 2019
Resort at Squaw Creek
North Lake Tahoe, California

Course Chairs
Robert B. Baron, MD, MS
University of California, San Francisco

University of California, San Francisco School of Medicine
Exhibitors

Wolterskluwer
Essentials of Primary Care
A core Curriculum for Ambulatory Practice

Educational Objectives
The purpose of this course is to increase competence and improve clinician practice in primary care. We specifically anticipate improvements in skills and strategies to:

- Implement new guidelines in office-based preventive medicine including cancer screening and management of cardiac risk factors;
- Develop strategies to care for common office problems including hypertension, lipid disorders, diabetes, coronary heart disease, heart failure, chronic kidney disease, Parkinson’s Disease, sleep disorders, and sexually transmitted infections;
- Manage common problems in women’s health including osteoporosis, contraception, and menopause;
- Diagnose and treat common skin disorders, skin infections, and skin cancer;
- Manage common problems in psychiatry including depression, bipolar disorder, anxiety, and somatoform disorders;
- Manage common problems in geriatrics;
- Counsel patients to improve eating habits, lose weight, and increase physical activity;
- Perform an effective problem-focused history and physical examination for evaluation and treatment of dermatologic complaints;
- Perform common office procedures in dermatology and office gynecology;
- Develop best practices in patient communication;
- Critically evaluate the medical literature and apply it to clinical practice;
- Increase quality and decrease costs in medical practice.

Accreditation
The University of California, San Francisco School of Medicine (UCSF) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

UCSF designates this live activity for a maximum of 20.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity meets the requirements under California Assembly Bill 1195, Continuing Education and Cultural and Linguistic Competency.
Geriatric Medicine
The approved credits shown above include 15.75 geriatric credits toward meeting the requirement under California Assembly Bill 1820, Geriatric Medicine.

Pharmacy
The California Board of Pharmacy accepts as continuing professional education those courses that meet the standard of relevance to pharmacy practice and have been approved for *AMA PRA Category 1 Credit™*.

Nurses
For the purpose of recertification, the American Nurses Credentialing Center accepts *AMA PRA Category 1 Credits™* issued by organizations accredited by the ACCME.

Pharmacotherapeutics CEUs for Nurses
For the purposes of recertification the American Nurses Credentialing Center accepts *AMA PRA Category 1 Credits™* issued by organizations accredited by the ACCME. This activity is designated for a maximum of 14.25 pharmacotherapeutic credits towards meeting the requirement for nursing pharmacology continuing education. Nurses should claim 0.1 CEUs for each contact hour of participation in designated pharmacotherapeutic continuing education.

Physician Assistants
AAPA accepts category 1 credit from AOACCME, Prescribed credit from AAFP, and *AMA PRA Category 1 Credits™* from organizations accredited by the ACCME.

Maintenance of Certification
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 20.25 MOC points in the American Board of Internal Medicine’s (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider’s responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

**IMPORTANT:** The online course evaluation must be completed by the due date specified - no exception. Within 45 days after submitting your evaluation, we will report your MOC points.

Family Physicians
This Live activity, Essentials of Primary Care: A Core Curriculum for Ambulatory Practice, with a beginning date of 08/04/2019, has been reviewed and is acceptable for up to 19.25 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
General Information

Attendance Verification/Sign-In Sheet / CME Certificates
Please remember to sign-in on the sign-in sheet when you check in at the UCSF Registration Desk on your first day. You only need to sign-in once for the course, when you first check in.

After the meeting, you will receive an email from Qualtrics@ucsf.edu with a link to complete your online Course Evaluation/ Electronic CME Certificate. Please make sure that you add this email to your safe senders list. The Qualtrics system will send you reminders to complete your CME Certificate Claiming until you complete it.

Upon completing the Electronic CME Certificate, your CME certificate will be automatically generated to print and/or email yourself a copy. For smartphone users, you may want to take a photo of your certificate as some settings prevent you from emailing the certificate.

The link will be available for 30 days after the last day of the course. However, after that date the link will expire and you will no longer be able to claim your credits online. You must then contact the Office of CME at registration@ocme.ucsf.edu to receive your certificate.

Speaker Survey
Your opinion is important to us – we do listen! The speaker survey is the bright yellow hand-out you received when you checked in. Please complete this during the meeting and turn it in to the registration staff at the end of the course.

Security
We urge caution with regard to your personal belongings and syllabus books. We are unable to replace these in the event of loss. Please do not leave any personal belongings unattended in the meeting room during lunch or breaks or overnight.

Exhibits
Industry exhibits will be available outside the ballroom during breakfasts and breaks, and lunches.

Final Presentations
A link to PDF versions of the final presentations will be sent via e-mail approximately 3 – 4 weeks post course. Only presentations that have been authorized for inclusion by the presenter will be included.
Federal and State Law
Regarding Linguistic Access and Services for Limited English Proficient Persons

I. Purpose.
This document is intended to satisfy the requirements set forth in California Business and Professions code 2190.1. California law requires physicians to obtain training in cultural and linguistic competency as part of their continuing medical education programs. This document and the attachments are intended to provide physicians with an overview of federal and state laws regarding linguistic access and services for limited English proficient (“LEP”) persons. Other federal and state laws not reviewed below also may govern the manner in which physicians and healthcare providers render services for disabled, hearing impaired or other protected categories.

The Federal Civil Rights Act of 1964, as amended, and HHS regulations require recipients of federal financial assistance (“Recipients”) to take reasonable steps to ensure that LEP persons have meaningful access to federally funded programs and services. Failure to provide LEP individuals with access to federally funded programs and services may constitute national origin discrimination, which may be remedied by federal agency enforcement action. Recipients may include physicians, hospitals, universities and academic medical centers who receive grants, training, equipment, surplus property and other assistance from the federal government.

HHS recently issued revised guidance documents for Recipients to ensure that they understand their obligations to provide language assistance services to LEP persons. A copy of HHS’s summary document entitled “Guidance for Federal Financial Assistance Recipients Regarding Title VI and the Prohibition Against National Origin Discrimination Affecting Limited English Proficient Persons – Summary” is available at HHS’s website at: http://www.hhs.gov/ocr/lep/.

As noted above, Recipients generally must provide meaningful access to their programs and services for LEP persons. The rule, however, is a flexible one and HHS recognizes that “reasonable steps” may differ depending on the Recipient’s size and scope of services. HHS advised that Recipients, in designing an LEP program, should conduct an individualized assessment balancing four factors, including: (i) the number or proportion of LEP persons eligible to be served or likely to be encountered by the Recipient; (ii) the frequency with which LEP individuals come into contact with the Recipient’s program; (iii) the nature and importance of the program, activity or service provided by the Recipient to its beneficiaries; and (iv) the resources available to the Recipient and the costs of interpreting and translation services.

Based on the Recipient’s analysis, the Recipient should then design an LEP plan based on five recommended steps, including: (i) identifying LEP individuals who may need assistance; (ii) identifying language assistance measures; (iii) training staff; (iv) providing notice to LEP persons; and (v) monitoring and updating the LEP plan.

A Recipient’s LEP plan likely will include translating vital documents and providing either on-site interpreters or telephone interpreter services, or using shared interpreting services with other Recipients. Recipients may take other reasonable steps depending on the emergent or non-emergent needs of the LEP individual, such as hiring bilingual staff who are competent in the skills required for medical translation, hiring staff interpreters, or contracting with outside public or private agencies that provide interpreter services. HHS’s guidance provides detailed examples of the mix of services that a Recipient should consider and implement. HHS’s guidance also establishes a “safe harbor” that Recipients may elect to follow when determining whether vital documents must be translated into other languages. Compliance with the safe harbor will be strong evidence that the Recipient has satisfied its written translation obligations.

In addition to reviewing HHS guidance documents, Recipients may contact HHS’s Office for Civil Rights for technical assistance in establishing a reasonable LEP plan.
The California legislature enacted the California’s Dymally-Alatorre Bilingual Services Act (Govt. Code 7290 et seq.) in order to ensure that California residents would appropriately receive services from public agencies regardless of the person’s English language skills. California Government Code section 7291 recites this legislative intent as follows:

“The Legislature hereby finds and declares that the effective maintenance and development of a free and democratic society depends on the right and ability of its citizens and residents to communicate with their government and the right and ability of the government to communicate with them.

The Legislature further finds and declares that substantial numbers of persons who live, work and pay taxes in this state are unable, either because they do not speak or write English at all, or because their primary language is other than English, effectively to communicate with their government. The Legislature further finds and declares that state and local agency employees frequently are unable to communicate with persons requiring their services because of this language barrier. As a consequence, substantial numbers of persons presently are being denied rights and benefits to which they would otherwise be entitled.

It is the intention of the Legislature in enacting this chapter to provide for effective communication between all levels of government in this state and the people of this state who are precluded from utilizing public services because of language barriers.”

The Act generally requires state and local public agencies to provide interpreter and written document translation services in a manner that will ensure that LEP individuals have access to important government services. Agencies may employ bilingual staff, and translate documents into additional languages representing the clientele served by the agency. Public agencies also must conduct a needs assessment survey every two years documenting the items listed in Government Code section 7299.4, and develop an implementation plan every year that documents compliance with the Act. You may access a copy of this law at the following url: http://www.spb.ca.gov/bilingual/dymallyact.htm
## Course Chairs

Robert B. Baron, MD, MS  
Professor of Medicine;  
Associate Dean for Graduate and Continuing Medical Education  
University of California, San Francisco

## Course Faculty (University of California, San Francisco unless indicated)

Descartes Li, MD  
Professor of Psychiatry; Director, UCSF Bipolar Disorder Program; Director, Medical Student Education, UCSF Department of Psychiatry

Toby A. Maurer, MD  
Professor of Dermatology; Chief of Dermatology, Zuckerberg San Francisco General

Michael S. Policar, MD, MPH  
Professor Emeritus of Obstetrics, Gynecology and Reproductive Sciences

Leah S. Karliner, MD, MAS  
Professor of Medicine; Director, Center on Aging in Diverse Communities

Michael G. Shlipak, MD, MPH  
Professor of Medicine, Epidemiology & Biostatistics; Associate Chief of Medicine for Research Development, San Francisco VA Medical Center

Judith M.E. Walsh, MD, MPH  
Professor of Medicine, Women’s Health Clinical Research Center
The following faculty speakers, moderators, and planning committee members have disclosed they have no financial interest/arrangement or affiliation with any commercial companies who have provided products or services relating to their presentation(s) or commercial support for this continuing medical education activity:

Robert Baron, MD, MS  
Leah S. Karliner, MD, MAS  
Descartes Li, MD  
Toby A. Maurer, MD  
Judith M.E. Walsh, MD, MPH

The following faculty speakers have disclosed a financial interest/arrangement or affiliation with a commercial company who has provided products or services relating to their presentation(s) or commercial support for this continuing medical education activity. All conflicts of interest have been resolved in accordance with the ACCME Standards for Commercial Support:

Michael Policar, MD, MPH  
Bayer Consultant  
Sebela Pharmaceuticals Independent Contractor

Michael Shlipak, MD, MPH  
TAI Diagnostics Advisor or Reviewer  
Cricket Health Stock Shareholder (excluding mutual funds)  
Grant/Research Support  
Advisor or Reviewer

This UCSF CME educational activity was planned and developed to: uphold academic standards to ensure balance, independence, objectivity, and scientific rigor; adhere to requirements to protect health information under the Health Insurance Portability and Accountability Act of 1996 (HIPAA); and, include a mechanism to inform learners when unapproved or unlabeled uses of therapeutic products or agents are discussed or referenced.

This activity has been reviewed and approved by members of the UCSF CME Governing Board in accordance with UCSF CME accreditation policies. Office of CME staff, planners, reviewers, and all others in control of content have disclosed no relevant financial relationships.
COURSE PROGRAM

Sunday, August 4, 2019

3:00 pm  Registration and Check-In
Moderator: Robert B. Baron, MD, MS

5:00pm  Welcome and Course Overview
Robert B. Baron, MD, MS

5:10  G  Controversies in Cancer Screening 2019: Colon, Breast, Lung, and Prostate
Judith M.E. Walsh, MD, MPH

6:00  G  Controversies in Cancer Screening 2019: Cervical, Ovarian and the Well Women Exam
Michael S. Policar, MD, MPH

6:50 pm  Adjourn

Monday, August 5, 2019

7:00 am  Registration and Continental Breakfast
Moderator: Robert B. Baron, MD, MS

7:30  RxG  Management of Lipid Disorders: Integrating the New Guidelines
Robert B. Baron MD MS

8:20  RxG  Management of Coronary Artery Disease: A Primary Care Perspective
Michael G. Shlipak, MD, MPH

9:10  Coffee Break

9:30  RxG  Common Dermatologic Problems: What the Primary Care Physician Needs to Know
Toby A. Maurer, MD

10:20  RxG  Update on Sexually Transmitted Infections
Michael S. Policar, MD, MPH

11:10 am  Adjourn

Tuesday, August 6, 2019

7:00 am  Registration and Continental Breakfast
Moderator: Judith M.E. Walsh, MD, MPH

7:30  RxG  Current and Emerging Strategies for Osteoporosis
Judith M.E. Walsh, MD, MPH

8:20  RxG  Skin Diseases in the Aging Patient
Toby A. Maurer, MD

9:10  RxG  Depression in Primary Care: Mourning or Melancholia?
Descartes Li, MD

10:00  Coffee Break

10:20  Concurrent Workshops (Select One)
A: Dermatologic Procedures in Primary Care
Toby A. Maurer, MD

B: Advances in Women’s Health: A Critical Review of the Year’s Most Important Papers
Judith M.E. Walsh, MD, MPH

11:50 am  Adjourn

Rx = Meets Requirements for Pharmacotherapeutics CEUs for NPs/Nurses
T = Trauma Credit
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Moderator: Leah S. Karliner, MD, MAS

7:30  RxG  Evaluating and Treating Parkinson's Disease and Tremors  Leah S. Karliner, MD, MAS

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C: Somatic Symptom Disorder and Related Disorders: Clinical Pearls in Assessment and Treatment  Descartes Li, MD

D: Obesity and Weight Management in Office Practice  Robert B. Baron, MD, MS

11:50 am  Adjourn

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Moderator: Michael S. Policar, MD, MPH

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F: Should It Change Your Practice? A Deeper Look at Some of the Past Year's Most Important Papers  Michael G. Shlipak, MD, MPH

11:50 am  Adjourn

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10:20  RxG  Managing Sleep and Its Disorders: Beyond Sleep Hygiene  Descartes Li, MD

11:10 am  Adjourn

Rx = Meets Requirements for Pharmacotherapeutics CEUs for NPs/Nurses
T = Trauma Credit
Cancer Screening 2019

New Recommendations,
New Controversies

Judith M.E. Walsh, MD, MPH
Division of General Internal Medicine
Women’s Health Center of Excellence
University of California, San Francisco

Disclosures

• I have no conflicts of interest
Selected Controversies

• Breast Cancer Screening
  – Guideline confusion
  – Implications of “dense breasts”
  – New screening technologies

• Colorectal Cancer
  – What test and how often?
  – New options?

Selected Controversies

• Lung Cancer
  – Why not Chest X Ray?
  – Who should we screen?

• Prostate Cancer
  – The ongoing question- should we screen?
But what about?

- Cervical Cancer and HPV screening
- Ovarian Cancer Screening?
- Pelvic Exam?
  - Stay tuned!!!!

Principles of screening

- Detection while patient is asymptomatic
  - High sensitivity
- Early detection reduces the risk of death from the cancer – randomized trials
- The number of false positives is acceptably low
  - High specificity
  - Reasonably high prevalence of disease
- Ideally few harms
USPSTF

• Rigorous review of existing peer-reviewed evidence
• Ratings reflect the strength of the evidence on the benefits and harms of a preventive service
• No consideration of costs
• ACA: Must cover A or B ratings

USPSTF Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High certainty of substantial net benefit</td>
<td>Provide</td>
</tr>
<tr>
<td>B</td>
<td>High certainty of moderate net benefit Moderate certainty of moderate/substantial net benefit</td>
<td>Provide</td>
</tr>
<tr>
<td>C</td>
<td>Moderate certainty that net benefit is small</td>
<td>Selectively offer/provide</td>
</tr>
<tr>
<td>D</td>
<td>No net benefit or harms outweigh benefits</td>
<td>Do not provide</td>
</tr>
<tr>
<td>I</td>
<td>Insufficient evidence regarding balance of benefits and harms</td>
<td></td>
</tr>
</tbody>
</table>

Page 4
Breast Cancer Screening

- Breast cancer is the most common cancer in women and the second leading cause of cancer death
- Screening mammography reduces breast cancer mortality
- Risk increases with age
- Pre-menopausal breast tissue is dense – Decreased sensitivity

Breast Cancer Screening

- Maggie Graham is a 52 year old woman with no family history of breast cancer. Her last mammogram showed “dense breast tissue” and she was told to discuss next steps, with you her PCP.
- You perform a clinical breast examination, which is normal.
**Breast Cancer Screening**

- **What do you recommend to Maggie?**
  - Breast ultrasound and mammogram
  - Breast MRI and mammogram
  - Digital breast tomosynthesis
  - Standard digital mammography

**U.S. screening guidelines: no agreement**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Starting age</th>
<th>Stopping age</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Preventive Services Task Force (USPSTF)</td>
<td>50</td>
<td>74</td>
<td>Biennially</td>
<td>Screening for age 40-49 = Grade C recommendation</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>45</td>
<td>As appropriate based on life expectancy</td>
<td>Annually, then biennially once age ≥55</td>
<td>Continue screening as long as good health, life expectancy &gt; 10 years.</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists (ACOG)</td>
<td>40</td>
<td>As appropriate based on life expectancy</td>
<td>Annually</td>
<td>Consider cessation of screening at age 75.</td>
</tr>
</tbody>
</table>
### USPSTF vs American Cancer Society Recommendations

<table>
<thead>
<tr>
<th>Age</th>
<th>USPSTF 2015</th>
<th>ACS 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>None (or biennial)</td>
<td>None</td>
</tr>
<tr>
<td>45-49</td>
<td>None (or biennial)</td>
<td>Annual</td>
</tr>
<tr>
<td>50-54</td>
<td>Biennial</td>
<td>Annual</td>
</tr>
<tr>
<td>55-74</td>
<td>Biennial</td>
<td>Biennial</td>
</tr>
<tr>
<td>75+</td>
<td>Insufficient evidence for or against</td>
<td>Biennial if good health and life expectancy ≥10 yrs</td>
</tr>
</tbody>
</table>

American Cancer Society Guidelines. JAMA 2015;314(15):1599-1614

### When to start

- Age is the most important risk factor for breast cancer
- Because of lower prevalence, screening younger women leads to many more false positives
- Younger women have denser breasts
  - Mammography quality
Harms Of Screening

• Over-diagnosis
  – Cancers diagnosed that never would cause symptoms: patients receive all the costs and harms of treatment
  – Estimates: 10% to 30% of invasive breast cancers plus much of DCIS

• False positives
  – Anxiety
  – Additional tests including biopsies
  – One-third of total screening cost

• Radiation exposure
  – One breast cancer for 3000 women screened annually for 10 years

Jorgensen, BMJ, 2009

Impact of mammographic screening in U.S.

Welch NEJM 2013
Screening has also led to large increase in detection of ductal carcinoma in situ (DCIS)

Figure 2. SEER9 Age-adjusted incidence rate of breast cancer by stage (1973-2005)

Breast Cancer Deaths Randomized Trials, all ages

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Deaths Averted Screening 1,000 Women Over 10 Years</th>
<th>95% confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 49</td>
<td>0.3</td>
<td>0 to 0.9</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.8</td>
<td>0.2 to 1.7</td>
</tr>
<tr>
<td>60 to 69</td>
<td>2.1</td>
<td>1.1 to 3.2</td>
</tr>
<tr>
<td>70 to 74</td>
<td>1.3</td>
<td>0 to 3.2</td>
</tr>
<tr>
<td>75+</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td>50 to 69</td>
<td>1.3</td>
<td>0.6 to 0.2</td>
</tr>
</tbody>
</table>

Bottom line: Greatest screening benefit in women aged 60-69; smaller, and possibly no, screening benefit in women aged 40-49
False-Positive Results and Breast Biopsies per 1000 women

<table>
<thead>
<tr>
<th>Harms of One-Time Mammography Screening, by age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>False-positive mammogram</td>
</tr>
<tr>
<td>Breast biopsies recommended</td>
</tr>
<tr>
<td>Biopsies per cancer diagnosed</td>
</tr>
</tbody>
</table>

Estimated annual mammography screening costs in the US

Screening the 40 million women in the US aged 50-74 costs $4.72 billion per year

Screening the 22 million women in the US aged 40-49 costs an additional $1.32 billion per year

State breast density legislation

• Requires notification of women with *heterogeneously dense* or *extremely dense* breasts
• Exact wording specified by law: decreased sensitivity and increased risk for BC
• No mandate for insurance coverage of supplemental screening in most states

Breast Screening Technologies

• Digital Mammography
• Digital Breast Tomosynthesis
• Breast MRI
• Breast Ultrasound
Digital mammography

- Standard of care now
- Compared with film mammography, higher sensitivity, same specificity in women < 50 years old, dense breasts
  - Sensitivity 78% versus 51% film
  - Specificity 90%
- Worse in women 65 and older
  - Sensitivity 53% versus 69% film

Digital Breast Tomosynthesis

- Digital Breast Tomosynthesis (DBT) as a primary screening strategy

![Digital Breast Tomosynthesis Diagram]

http://www.nydailynews.com/
USPSTF: DBT

- Digital Breast Tomosynthesis (DBT) as a primary screening strategy
  - Benefit: Reduces recall rate and increases cancer detection rates compared to conventional mammography
  - Harm: twice as much radiation; unknown rate of over diagnosis. May increase biopsy rates

- No evidence on mortality, morbidity, or QOL
- “Insufficient evidence to fully assess benefits and harms”
MRI Screening

• Does MRI have a role for screening in high risk women?
  – MRI is a very sensitive method of breast imaging and has been used as a diagnostic tool in women with breast cancer
  – Not influenced by breast density
  – Specificity is variable
  – Expensive

Supplemental screening: better outcomes?

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Ultrasound (US)</th>
<th>Tomosynthesis (DBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Most sensitive</td>
<td>Well-tolerated</td>
<td>Similar cancer detection rate, fewer false positives</td>
</tr>
<tr>
<td></td>
<td>No radiation</td>
<td>Relatively inexpensive</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>High false positive rate</td>
<td>High false positive rate (low PPV)</td>
<td>Not as sensitive as MRI</td>
</tr>
<tr>
<td></td>
<td>Overdiagnosis</td>
<td>Operator-dependent</td>
<td>Limited evidence base (newer)</td>
</tr>
<tr>
<td></td>
<td>IV contrast</td>
<td></td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td>Claustrophobia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Expensive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

USPSTF Grade I: January 2017
**Impact For Clinical Practice**

- MRI may be useful in screening high risk women
- The effect of MRI screening on mortality is not known
- MRI is not currently recommended for screening average risk women
- Ultrasound adds little to mammography
- Tomosynthesis is promising

**Bottom Line: Breast Cancer**

- 40-49 informed consent
  - Digital if decide to screen: now standard
- 50-74 screen every 2 years
- 75+ informed consent – not if life expectancy less than 10 years
- Don’t promote SBE, promote breast awareness
- BRCA risk equivalent: MRI
Lung Cancer Screening
Question?

- Ms. Virginia Slim is a 69 year old woman with a 50 pack-year history of smoking and COPD. You have previously been unsuccessful in encouraging her to quit smoking. She comes in for a check-up, is worried about developing lung cancer and wants to know what test you think he should have. What do you recommend?
  - Chest X ray
  - Sputum cytology
  - LDCT
  - None of these tests

What’s in your shopping cart?

IF YOU SMOKED:
This new lung cancer screening could save your life
Lung Cancer Screening: Systematic Review of Chest X-rays

- 7 trials of lung cancer screening
- Frequent screening with chest x-rays was associated with an increase in mortality
  - RR 1.11 (95% C.I. 1.00-1.23)
- No difference in chest X-ray plus cytology versus chest X-ray alone

Manser, Thorax, 2003

PLCO: Lung Cancer Screening

- PCLO randomly assigned 154,901 adults aged 55 through 74 to annual CXR for 4 years vs. usual care
- Followed for 13 years
- Cumulative lung cancer mortality
  - 14.0/10,000 py screening group vs. 14.2/10,000 py control group
  - Rate ratio: 0.99 (95% CI 0.87-1.22)

Oken MM. JAMA 2011;306:1865
Low Dose Spiral Computed Tomography

- Scans lung in < 20 seconds (single breath)
- No IV contrast
- More radiation exposure than CXR but less than conventional CT
- Can detect much smaller lesions than chest X-ray

The National Lung Screening Trial (NLST)

53,454 participants randomized to CT or CXR
- Current or former heavy smokers: ≥ 30 pack-years
- Ages 55 to 74
- Annual CT scans x 3 years. 6.5 years follow-up

<table>
<thead>
<tr>
<th>Event</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer death</td>
<td>.80 (.73-.93)</td>
</tr>
<tr>
<td>Any death</td>
<td>.93 (.86-.98)</td>
</tr>
</tbody>
</table>

20% reduction in lung cancer death; 7% all deaths!
Number needed to invite to screen

- NNI to prevent one lung cancer death in 6.5 years = 320
- NNI to prevent one death from any cause in 6.5 years = 218

Summary from NLST

<table>
<thead>
<tr>
<th>Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?</th>
<th>Low-dose CT 26,722 people</th>
<th>Chest X-ray 26,732 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 in 1,000 fewer died from lung cancer</td>
<td>13 in 1,000 versus 17 in 1,000</td>
<td></td>
</tr>
<tr>
<td>5 in 1,000 fewer died from all causes</td>
<td>70 in 1,000 versus 75 in 1,000</td>
<td></td>
</tr>
</tbody>
</table>

Harm: What problems did CT scans cause compared to chest X-ray?

<table>
<thead>
<tr>
<th>Harm</th>
<th>Low-dose CT 26,722 people</th>
<th>Chest X-ray 26,732 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>223 in 1,000 more had at least one false alarm</td>
<td>365 in 1,000 versus 142 in 1,000</td>
<td></td>
</tr>
<tr>
<td>18 in 1,000 more had a false alarm leading to an invasive procedure, such as bronchoscopy, biopsy, or surgery</td>
<td>25 in 1,000 versus 7 in 1,000</td>
<td></td>
</tr>
<tr>
<td>2 in 1,000 more had a major complication from invasive procedures</td>
<td>3 in 1,000 versus 1 in 1,000</td>
<td></td>
</tr>
</tbody>
</table>
NLST Harms

- False positives
  - At least 1 positive test in 39% CT
- Possible over diagnosis
  - Higher cancer incidence with CT
    - 1060 vs. 941 cancers
    - Rate ratio 1.13 (95% CI 1.03-1.23)
- Radiation exposure
- Incidental findings

**Annals of Internal Medicine**

**Ideas and Opinions**

*When the Average Applies to No One: Personalized Decision Making About Potential Benefits of Lung Cancer Screening*

Peter B. Bach, MD, MAPP, and Michael K. Gould, MD, MS

**Table:** Projected Likelihood Over 6 Years of Lung Cancer Death With or Without Screening per 1000 Persons Screened

<table>
<thead>
<tr>
<th>Participant</th>
<th>Risk Factors</th>
<th>Deaths From Lung Cancer (Without Screening) per 1000 Persons, n</th>
<th>Deaths From Lung Cancer (With Screening) per 1000 Persons, n</th>
<th>Lung Cancer Deaths Averted per 1000 Persons, n</th>
<th>Persons Needed to Be Screened Annually for 3 y to Prevent 1 Death From Lung Cancer Over 6 y, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Typical&quot; participant in the NLST</td>
<td>62-year-old male current 1.5-PPD smoker for 35 y</td>
<td>19.5</td>
<td>15.6</td>
<td>3.9</td>
<td>256</td>
</tr>
<tr>
<td>Minimum eligible participant in the NLST</td>
<td>55-year-old female former 1-PPD smoker for 30 y who just quit</td>
<td>4.0</td>
<td>3.2</td>
<td>0.8</td>
<td>1236</td>
</tr>
<tr>
<td>High-risk participant eligible for the NLST</td>
<td>70-year-old current 2-PPD smoker for 55 y</td>
<td>60.9</td>
<td>48.7</td>
<td>12.2</td>
<td>82</td>
</tr>
<tr>
<td>Minimum eligible participant by NCCN guidelines</td>
<td>50-year-old male former 1-PPD smoker for 20 y who quit 10 y ago with an occupational asbestos exposure history</td>
<td>1.6</td>
<td>1.3</td>
<td>0.3</td>
<td>3180</td>
</tr>
<tr>
<td>Low-risk eligible participant for Sequoia Hospital lung screening program</td>
<td>40-year-old female former 1-PPD smoker for 10 y who quit 15 y ago</td>
<td>0.10</td>
<td>0.08</td>
<td>0.02</td>
<td>35186</td>
</tr>
</tbody>
</table>

NCCN = National Comprehensive Cancer Network; NLST = National Lung Screening Trial; PPD = packs per day.
* Assuming the program includes 3 annual y of screening.
The NLST Setting

- 76% of sites were NCI designated cancer centers
- 82% were large academic medical centers
- All likely to have specialized thoracic radiologists and board certified thoracic surgeons on site
- CT scanners extensive quality control
- Nodule management algorithm but not mandated

USPSTF Recommendation

- USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age and smoking history
  - Grade B recommendation
  - Published December 31, 2013
USPSTF

• Age
  – 55-79

• Total exposure to tobacco smoke
  – 30 pack years or more

• Years since quitting
  – Those who have smoked within the past 15 years are at highest risk

• Consider other comorbidities

Medicare Coverage Decision

• Annual lung cancer screening with LDCT for age 55-77, asymptomatic, at least 30 pack year history and currently smoking or quit within past 15 years

• Written order for lung cancer screening written during lung cancer screening shared decision making visit furnished by physician or certified non-physician practitioner

  – February, 2015
Primary Prevention Of Lung Cancer

- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation!!!!!

Implications

- Smoking cessation
- Strict adherence to guidelines
  - 55-79 years, 30+ pack years
- Use experienced centers / demonstration projects to ensure quality and effectiveness
Colorectal Cancer

Question

• What do you most commonly recommend for colorectal cancer screening?
  – Fecal occult blood test (FOBT)
  – Fecal immunochemical Test (FIT)
  – Sigmoidoscopy
  – Colonoscopy
  – Virtual Colonoscopy
  – Fecal DNA
Guidelines

Multi-Society Guidelines

- American College of Gastroenterology, American Gastroenterological Association, Society for Gastrointestinal Endoscopy
- New guidelines include three “tiers” of testing
  - Start with the top tier and then move down

July, 2017
Multi-Society Guidelines

• First tier tests
  – Colonoscopy or FIT
  – Offer colonoscopy first
  – A risk stratified approach is also appropriate

• Second tier tests
  – CT colonography every 5 years
  – FIT-fecal DNA every 3 years
  – Sigmoidoscopy every 5-10 years

• Third tier
  – Capsule colonoscopy every 5 years

• Septin 9 is not recommended

• Start screening at age 50 in average risk individuals
  – Limited evidence supports screening African Americans starting at age 45

• Consider discontinuing screening at age 75 or less than 10 years life expectancy
American College of Physicians 2015

- Annual high sensitivity gFOBT or FIT
- Flex sigmoidoscopy every 5 years
- High sensitivity gFOBT or FIT every 4 years plus flex sigmoidoscopy every 5 years
- Colonoscopy every 10 years

» Ann Int Med 2015

USPSTF 2016

- USPSTF: “A” recommendation (2016)
  - Routine screening from age 50 until 75
- USPSTF “C” recommendation (2016)
  Individualized decisions age 76 to 85
  - Greater benefit in those not previously screened
- No screening after 85

USPSTF JAMA 2016
USPSTF 2016

• Screening for CRC in average risk patients age 50-75 is of substantial net benefit

• Multiple screening strategies available
  – Different levels of evidence
  – Strategies reviewed include colonoscopy, FOBT, FIT, flex sig, CT colonography, fecal DNA and methylated SEPT9DNA test
  – No evidence that any strategy provides greater net benefit

ACS 2018

• Adults age 45 and older at average risk should have screening with stool based test or structural test
  – Starting at age 45 “qualified recommendation”
  – Starting at age 50 “strong recommendation”
  – All positive results on noncolonoscopy screening tests followed by colonoscopy

• Continue screening up to age 75 if in good health and > 10 year life expectancy

• Individualize decisions for those aged 75-85

• Discourage routine screening in those over 85
Colonoscopy: RCTs in progress

• VA
  – Colonoscopy versus fecal immunochemical test in reducing mortality from colorectal cancer
• Spain
  – Colorectal cancer screening in average-risk population: immunochemical fecal occult blood testing versus colonoscopy
• Netherlands
  – Colonoscopy or colonography for screening

Newer Tests

• Virtual Colonoscopy
• Stool based molecular testing
  – Fecal DNA
• Combined FIT and Stool DNA
• Septin-9
Computed Tomographic Colonography (Virtual Colonoscopy)

- Non-invasive radiological technique
  - Radiation dose similar to barium enema
- Bowel preparation similar to colonoscopy
  - Prep-less technique is being evaluated
- Does not require sedation
- Colon distended with carbon dioxide or air
- Breath holding for 20-50 seconds
- Colonoscopy to remove polyps

Laxative-Free CT Colonography

- Low fiber diet, orally ingested contrast material and specialized processing software “electronic cleansing”
- 605 adults underwent CTC and OC
- CTC was more accurate in detecting adenomas 10 mm or larger and less so for smaller lesions
  - 91% sensitivity vs 70% for adenoma 8 mm or larger
- Patients preferred it

Potential Harms

• Radiation Exposure
  – 1/1000 could develop solid cancer or leukemia

• Procedure related harms
  – Perforation rate low

• Extra-colonic findings

Extra-colonic Findings

• Extra-colonic findings common: 27 – 69%

• “High” clinical significance require surgical or medical treatment or intervention or further investigation
  – 5 - 11%

• 7-16% of individuals need additional evaluation for extra-colonic findings, but very few abnormalities ultimately required definitive treatment
Fecal DNA Testing

- PCR test for DNA mutations in the stool
- Potential advantages
  - Non-invasive
  - No preparation
  - Detection along entire length of the colon

Multi-target Stool DNA Testing

- Multi-target DNA test (and hemoglobin), FIT, and colonoscopy 9989 average risk adults in multiple centers
- Fecal DNA detects more neoplasms than FIT, but with more false positive results
  - Sensitivity for CRC 92.3% vs 73.8%
  - Specificity for CRC 86.6% vs 94.9%
- Problems with sample collection or assay application greater with DNA test
  - 6.3% vs 0.3%

Imperiale, 2014
Fecal Immunochemical Testing (FIT)

- Uses labeled antibodies that attach to antigens of any human globin present in the stool
- Globin does not survive passage of the upper GI tract
- No dietary restrictions (easier than FOBT)

Fecal Immunochemical Testing

- FIT is more sensitive in detecting CRC and large adenomas (>1 cm) than FOBT
- FIT is a little less specific than FOBT
Combined FIT-Stool DNA

- Cologuard is the only combined stool DNA with FIT available in the U.S.
- Colorectal cancer detection
  - Sensitivity 92%
  - Specificity 84%
- More sensitive than FIT but less specific
  - More false positives

Septin 9

- Second generation serum assay to detect circulating Septin 9
  - Septin 9 hypermethylated in CRC
  - FDA approved 2016
- Use for those refusing guideline recommended strategies?
  - Multi-society task force does not recommend it
Colorectal Cancer Screening: Choices

- Randomized trial offering colonoscopy, FOBT, or choice of colonoscopy/FOBT
- 997 subjects ages 50 to 79
- 12-month follow up
  - (Inadomi JM. Arch Intern Med 2012;172:575)
- Recommending only colonoscopy led to lower adherence

Screening Completion

![Chart showing adherence rates for FOBT, COLO, and CHOICE methods.](Inadomi JM. Arch Intern Med 2012;172:575)
Colorectal Cancer Screening: Conclusions

- Offer testing
- Any screening is better than no screening for reducing colorectal cancer mortality
- Increase awareness of the importance of colorectal cancer screening
Implications for Practice

- Recognize importance of patient preferences
  - “The best test is the one that gets done”
- Positive fecal blood tests must be evaluated with diagnostic colonoscopy

QUESTION

- What is your usual practice for PSA screening for men aged 50-70?
  - Usually order PSA
  - Sometimes order PSA
  - Rarely order PSA
  - Never order PSA
Prostate Cancer: Should We Screen?

- Disease has high prevalence
  - 10% lifetime risk
  - 30% of men have prostate cancer at autopsy
- Disease has serious consequences
  - Sometimes but may be a benign disease for many men
- Detectable preclinical phase- ?? PSA
- Treatment for preclinical disease is more effective?
  - Complications of prostate cancer treatment
    - 8.4% incontinence
    - 60% impotence
      » Prostate Cancer Outcomes Study 24 month follow up Screening
- Screening reduces cancer mortality?

SCREENING TESTS: PSA

- PSA testing has increased dramatically since 1988
- Observational studies have had conflicting findings about the benefits of screening
- Three large randomized controlled trials of PSA screening and mortality
PLCO Cancer Screening Trial

- 76,693 men randomized to annual PSA for 6 years plus rectal examination for four years vs usual care
- High rates of screening in the control group
- No significant difference in death between the two groups at 7 year follow-up
  - 2.0 deaths per 10,000 person years in the screening group
  - 1.7 deaths per 10,000 person years in the controls
- Similar results after 10 years
  - Andriole, NEJM 2009

European Randomized Study of Screening for Prostate Cancer (ERSPC)

- 182,160 men aged 50-74 in eight European countries
- PSA screening at least once every four years vs no screening
- Mortality lower in the screened group at 9 year follow up
  - 7 fewer prostate cancers per 10,000 screened men
- To prevent one prostate cancer death at 11 year follow up
  - 1,410 men needed to be screened
  - 48 additional prostate cancers treated
- To prevent one prostate cancer death at 13 year follow up
  - 781 men screened
Question?

• Could we reduce the harms of over-diagnosis and over-treatment by less intensive screening?

CAP Study

• Effect of a low-intensity PSA based screening intervention on prostate cancer mortality: The CAP randomized clinical trial.
  – Martin et al. JAMA 2018

• Objective: To evaluate the impact of a single PSA testing intervention and standardized diagnostic pathway on prostate cancer mortality
Methods

• Cluster Randomized Trial
  – 573 primary care practices in United Kingdom
  – 419,582 men aged 50 yo 69

• Intervention:
  – Single PSA test vs standard of care

• Primary Outcome:
  – Prostate Cancer mortality

Results

• 40% of those invited attended PSA testing clinic

• 11% had a PSA result between 8.0 and 19.9 ng/ml
  – 85% had biopsy

• No reduction in prostate cancer mortality after 10 years
  – 0.3 vs 0.31 per 1000 person years
Seek and you shall find.

Results

• More diagnosed with prostate cancer in the intervention group
  – 4.3% vs 3.6%: p<0.001

• More prostate cancers with Gleason grade 6 or lower in the intervention group
  – 17% vs 11%: p<0.001
PSA Screening: Conclusions

• PSA screening may lead to a modest reduction in mortality

• To achieve this mortality reduction, there is a substantial amount of over-diagnosis and over-treatment

USPSTF Recommendations 2012

• Recommended against PSA based screening for prostate cancer
  – PSA can detect early prostate cancer, but inconclusive evidence about whether early detection improves health outcomes.
  – Harms include frequent false positives and unnecessary anxiety, biopsies and potential complications of treatment of some cases of cancer that may never have affected a patient’s health.
  – Grade “D” recommendation

  — USPSTF 2012
USPSTF Recommendations 2017

- Clinicians should inform men age 55-69 about the potential benefits and harms of PSA screening
  - Grade C
- Decision to screen should be individualized
- No screening in men aged 70 and over
  - Grade D

USPSTF

- Persistent mortality reduction and new evidence to suggest decrease in metastatic prostate cancer with screening
  - 3 fewer cases per 1000 men over 13 years
- No specific recommendations for high risk men
  - Family history, African American
Men with at least a 10 year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened.

Screening should not occur without an informed decision making process.

Men at average risk should receive the information beginning at age 50.

Information should be provided at age 45 for men at higher risk and age 40 for very high risk.

For men unable to decide, the decision can be left to the discretion of the health care provider.

Men with less than a 10 year life expectancy should not be offered screening.

At age 75, only half of men have a life expectancy of 10 years or more.

Men without access to regular care should be tested only if high quality informed decision making is available through community based programs.

American Cancer Society, 2016

ACS 2016
American Cancer Society

- For those who choose to be screened
  - PSA with or without DRE
  - Screening yearly for men whose PSA is 2.5 ng/ml or greater
  - If PSA <2.5 ng/ml, screening can be extended to every 2 years
  - PSA of 4.0 ng/ml or greater- referral
  - PSA of 2.5-4.0 ng/ml individualized risk assessment
    - Age, African American, family history, previous negative biopsy
  » ACS, 2016

American Urological Association Guidelines

- The decision to use PSA testing should be individualized
  - Inform men of the potential benefits and risks
- No routine screening for men aged 40-54
- Shared decision making for men aged 55-69
- No routine screening for men aged 70 and over
- Screening intervals can be individualized based on baseline PSA level
  - American Urological Association, 2013
ACP Guidance Statement

• Derived from an appraisal of available guidelines
  – ACPM, ACS, AUA, USPSTF
• Inform men aged 50-69 about limited potential benefits and substantial harms of screening for PSA
  – Base decision on risk for prostate CA, discussion of benefits and harms, health and life expectancy and preferences
  – Do not screen in those who do not have a clear preference for screening

ACP Guidance Statement

• Do not screen average risk men under age 50, over age 69 or with a life expectancy of less than 10-15 years
Prostate Cancer Screening: Summary

• PSA testing may reduce prostate cancer mortality but the benefit is small
• Risks of early detection and treatment
• Shared decision making is key

Summary Of Recommendations

• Women aged 50 to 74 should undergo mammography every 2 years
• Screening decisions for women in their forties and for women and for women aged 75 and older should be individualized
• All men and women aged 50 -75 should be screened for colorectal cancer
  – Any screening is better than no screening
Summary Of Recommendations

- Screening for lung cancer with low-dose CT reduces mortality
  - USPSTF Recommends screening high risk individuals

- A shared decision making approach is recommended for prostate cancer screening

Questions?

“Today I ate two bowls of dog food, a sandwich crust, some spaghetti that fell on the floor, half of your cat food, a wet tea bag, three bugs and the inside of a sneaker. How many grams of fat is that?”
Current Strategies the Well-Woman Visit

Michael S. Policar, MD, MPH
Professor Emeritus of Ob, Gyn, and Repro Sci
UCSF School of Medicine
michael.policar@ucsf.edu

I have no disclosures relevant to this talk

General Disclosures
• Bayer: litigation consultant
• Sebela Pharmaceuticals:
  – Investigator proctor in phase III trial of a copper IUD (VeraCept)
Marisella

• 28 year old G₂P₀TAB₂ established client seen for a well woman visit
• In a monogamous relationship for the past two years
• Feeling well; no c/o vaginal discharge, abnormal bleeding, dyspareunia
• Last cervical cytology was 2 years ago in another city
• Currently using OCs; requests a year’s supply

Which screening tests does the USPSTF recommend?
What is the most important question to ask her?

Marisella: 28 Year Old Female

☐ Clinical breast exam
☐ Cervical cytology
☐ Bimanual pelvic exam
☐ Chlamydia + Gonorrhea NAAT
☐ HIV-1 serology
☐ HSV-2 serology
☐ Syphilis (VDRL or RPR)
☐ Hepatitis B serology
☐ Fasting blood glucose
☐ Fasting lipid profile
The Most Important Question To Ask?

• Do you have a primary care (or women’s health) provider?
  – When did you see her (or him)?
  – Which tests were performed? Results?

• Why is this so important?
  – Tailor the content of today’s visit
    • Comprehensive well woman visit, or
    • GYN health screening visit
  – Offer necessary services not yet performed
  – Avoid duplication of services already received
  – Minimize fragmentation of care

Historical Perspective

• “Check-ups” recommended in U.S. since the 1920s
• Now antiquated terms
  – Annual physical
  – Annual visit
  – Check-up visit
• Currently referred to as …
  – USPSTF: Periodic health screening visit
  – CPT: Preventive medicine visit
  – ACOG: Well woman visit (WWV)
The Well Woman Visit

• **Major health objectives**
  – Anticipatory guidance
  – Screening for asymptomatic conditions
  – Increase the client’s sense of well-being
  – Promote the clinician-client relationship
  – Positive action toward self-maintenance of health

• **In a family planning context**
  – Clarify her reproductive Intentions
  – Correct and consistent use of her contraceptive method
  – Optimize reproductive health

Who Defines Well Woman Services?

• **US Preventive Services Taskforce**
  – Primary care specialty societies (ACP, AAFP)
  – Most health plan guidelines

• **ACOG**: “Primary and Preventive Care” guidelines

• **ACS**: Cancer screening guidelines

• **OPA/CDC**: Providing Quality FP Services (QFP)

• **ACA**: Women’s Preventive Services
  – Benefits without cost-sharing; not practice guidelines
USPSTF 2007: Strength of Recommendation

<table>
<thead>
<tr>
<th>Comment</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Recommend</td>
<td>Net benefit is substantial</td>
</tr>
<tr>
<td>B Recommend</td>
<td>Net benefit is moderate</td>
</tr>
<tr>
<td>C Recommend against providing routinely</td>
<td>May be considerations that support the service in an individual patient</td>
</tr>
<tr>
<td>D Recommend against</td>
<td>No net benefit (or) harms outweigh benefits</td>
</tr>
<tr>
<td>I Evidence is insufficient</td>
<td>Evidence is lacking, poor quality, or conflicting</td>
</tr>
</tbody>
</table>

www.uspreventiveservicestaskforce.org

Well-Woman Recommendations

Annual assessments provide an excellent opportunity to counsel patients about preventive care and to provide or refer for recommended services. These assessments should include screening, evaluation and counseling, and immunizations based on age and risk factors. The interval for individual services varies.

These recommendations, based on age and risk factors, serve as a framework for care which may be provided by a single physician or a team of health care professionals. The scope of services provided by obstetrician-gynecologists in the ambulatory setting will vary from practice to practice. The recommendations should serve as a guide for the obstetrician-gynecologist and others providing health care for women and should be adapted as necessary to meet patients' needs. This information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Access recommendations on screening, laboratory testing, evaluation & counseling, or immunizations for a specific age range below:

<table>
<thead>
<tr>
<th>Ages 13–18</th>
<th>Ages 19–39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Screening</td>
</tr>
<tr>
<td>Laboratory and other tests</td>
<td>Laboratory and other tests</td>
</tr>
<tr>
<td>Evaluation &amp; counseling</td>
<td>Evaluation &amp; counseling</td>
</tr>
<tr>
<td>Immunizations</td>
<td>Immunizations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ages 40–64</th>
<th>Ages 65 Years and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
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</tr>
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ACOG

http://www.acog.org/
About-ACOG/ACOG-Departments/Annual-Womens-Health-Care/Well-Woman-Recommendations
Well Woman Visits

• Is a physical exam necessary with every WWV?
  – As needed for scheduled screening tests
  – Diagnostic exam when symptoms or signs
  – Some visits will consist solely of counseling and education without an exam beyond a BP check

• Is a yearly health screening visit advised if no tests are due?
  – USPSTF: every 1-3 years, depending upon health status and risk behaviors of the client
  – ACOG: perform annually

Exams and Tests Needed Before Contraceptive Method Initiation 2016

<table>
<thead>
<tr>
<th>Examination</th>
<th>Needed for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>OC, patch, ring</td>
</tr>
<tr>
<td>Weight (BMI) (weight [kg]/ height [m]²)</td>
<td>Hormonal methods</td>
</tr>
<tr>
<td>Bimanual examination, cervical inspection</td>
<td>IUC, cap, diaphragm</td>
</tr>
<tr>
<td>Clinical breast examination</td>
<td>None</td>
</tr>
<tr>
<td>Glucose, Lipids</td>
<td>None</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>None</td>
</tr>
<tr>
<td>Cervical cytology (Papanicolaou smear)</td>
<td>None</td>
</tr>
<tr>
<td>STD screening with laboratory tests</td>
<td>None</td>
</tr>
<tr>
<td>HIV screening with laboratory tests</td>
<td>None</td>
</tr>
</tbody>
</table>
Three Controversies in the Well Woman Visit

1. Reproductive goals counseling
2. Cervical cancer screening
3. Screening pelvic exam (SPE)

In the beginning, there was...

Reproductive Life Plan

“Plan” does not resonate with some women for cultural, religious, or socio-economic reasons
Reproductive Life Plan Questions

- Do you hope to have any (more) children?
- How many children do you hope to have?
- How long do you plan to wait until you become pregnant?
- How much space between your pregnancies?
- What do you plan to do until you are ready?
- What can I do today to help you achieve your plan?
Desires May be Ambivalent or Indifferent

- **Pro-natal**
  - Strong
- **Ambivalent**
- **Indifferent**
- **Anti-natal**

Desire to avoid pregnancy

Desire to become pregnant

Miller, Barber, & Gatny, 2013, *Population Studies*

Evolution if “One Key Question”

Would you like to become pregnant in the next year?

One Key Question®

Would You Like to Become Pregnant in the Next Year?

Do I want to become pregnant in the next year?
PATH (Pregnancy Attitudes, Timing, and How Important Is Pregnancy Prevention)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Attitude</td>
<td>• Do you think you might like to have (more) children at some point?</td>
</tr>
<tr>
<td>Timing</td>
<td>• When do you think that might be?</td>
</tr>
<tr>
<td>Resolve</td>
<td>• How important is it to you to prevent pregnancy until then?</td>
</tr>
</tbody>
</table>

### 2016 Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th></th>
<th>&lt;21 y.o.</th>
<th>21-29</th>
<th>30-65 y.o.</th>
<th>&gt;65</th>
<th>Hyst, benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF</td>
<td>[D]</td>
<td>Cytology every 3 y</td>
<td>Co-test: every 5 yr or Cytology: every 3 yr</td>
<td>None*</td>
<td>[D]</td>
</tr>
<tr>
<td>Triple A 2012</td>
<td>None</td>
<td>Cytology every 3 y</td>
<td>Co-test: every 5 yr or Cytology: every 3 yr</td>
<td>None*</td>
<td>None</td>
</tr>
<tr>
<td>ACOG 2016</td>
<td>“Avoid”</td>
<td>Cytology every 3 y</td>
<td>Co-test: every 5 yr or Cytology: every 3 yr</td>
<td>None*</td>
<td>None</td>
</tr>
</tbody>
</table>

* In adequately screened women (3 negative cytology results, or 2 negative co-tests, in prior 10 years, most recent within 5 years)
1° HPV Screening : Interim Guidance, 2015
(SGO, ASCCP, ACOG, ACS, others)

- If hrHPV testing alone
  - Screening should not be initiated before 25 years of age
  - Screen *no sooner* than every 3 years
- **Advantages**
  - Better sensitivity than cytology alone
  - Less expensive than co-testing (since no cytology for most)
  - Highly adaptable to low-resource countries
- **Disadvantages**
  - Less specificity than cytology alone...more colposcopies

**Cervical Cancer Screening**  
*Final Recommendation*  

2018

[A] Three options for women **30-65 years of age**....either  
– Primary hrHPV (only) every 5 years, OR  
– Co-testing every 5 years, OR  
– Cervical cytology alone every 3 years

[A] Women **21-29 years of age**: cytology every 3 years  
[D] Women **<21 years of age**: do not screen  
[D] Women **>65, adequately screened in prior 10 yrs, no history of treatment or NED >20 years**: do not screen

**Recommends that females discuss options with clinician**

---

### 2018 Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th></th>
<th>&lt; 21 y.o.</th>
<th>21-29 y.o.</th>
<th>30-65 y.o.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>USPSTF 2018</strong></td>
<td>[D]</td>
<td>Cytology every 3 yrs</td>
<td>hrHPV alone: every 5 yrs or Co-test: every 5 years or Cytology: every 3 yrs</td>
</tr>
<tr>
<td><strong>Triple A 2012</strong></td>
<td>None</td>
<td>Cytology every 3 yrs</td>
<td>Co-test: every 5 yrs or Cytology: every 3 yrs</td>
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<tr>
<td><strong>ACOG 2016</strong></td>
<td>“Avoid”</td>
<td>Cytology every 3 yrs</td>
<td>Co-test: every 5 yrs or Cytology: every 3 yrs</td>
</tr>
</tbody>
</table>

Co-test: cervical cytology plus high risk HPV test (hrHPV)  
Cytology: cervical cytology (Pap smear) alone
**Implications: 2018 USPSTF Cervical Cancer Screening Recommendations**

- ACOG, ACS & ASCCP haven’t changed recommendations yet, but may do so
- Fewer cervical cytology tests, since 1º hr-HPV screening option added in women ≥ 30 years of age
- More colposcopies, as women ≥30 years of age move away from cytology alone and toward 1º HPV screening
- Health plans may consider limiting the use of co-tests to surveillance after abnormal cytology or treatment

**Common Questions About Cytology Intervals**

- Do virginal women need to be screened?
- Are the intervals any different for women
  - With multiple sexual partners?
  - Using hormonal contraceptives, menopausal HT?
  - Who only have female partners?
  - Who are pregnant?
  - Who have been HPV vaccinated?
- If a cytology is *not* scheduled or necessary, what about the need to perform a screening bimanual pelvic exam?
Take it Home

<table>
<thead>
<tr>
<th>Michael Pollan: Healthy eating</th>
<th>Healthy Cervical Cancer Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eat food</td>
<td>Start later, end sooner</td>
</tr>
<tr>
<td>Not too much</td>
<td>Not too often</td>
</tr>
<tr>
<td>Mostly plants</td>
<td>Every 3 or 5 years</td>
</tr>
</tbody>
</table>

What doesn’t matter for screening intervals
• Age of sexual debut
• Prior HPV vaccination
• New sexual partners or practices
• Hormonal contraceptives or hormone therapy

2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

L. Stewart Massad, MD, Mark H. Einstein, MD, Warner K. Huh, MD, Hormuz A. Kattie, PhD, Walter K. Kinney, MD, Mark Schiffman, MD, Diane Solomon, MD, Nicolas Wentzensen, MD, and Herschel W. Lawson, MD, for the 2012 ASCCP Consensus Guidelines Conference

From Washington University School of Medicine, St. Louis, Missouri; Albert Einstein College of Medicine, New York; New York; University of Alabama School of Medicine, Birmingham, Alabama; Division of Cancer Epidemiology and Genetics and Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; The Permanente Medical Group, Sacramento, California, and Emory University School of Medicine, Atlanta, Georgia

Journal of Lower Genital Tract Disease, Volume 17, Number 5, 2013, S1-S27
### Cytology Alone

**Cytology every 3 y from ages 25-65 y**

<table>
<thead>
<tr>
<th>Abnormal test result</th>
<th>Recommended next steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US</td>
<td>Cytology in 1 y or hrHPV test hrHPV+ → Colposcopy hrHPV− → Cytology in 3 y</td>
</tr>
<tr>
<td>LSIL or worse</td>
<td>Colposcopy</td>
</tr>
</tbody>
</table>

Sawaya GF, JAMA 2019

### HPV Alone

**hrHPV testing alone every 5 y from ages 30-65 y**

<table>
<thead>
<tr>
<th>Abnormal test result</th>
<th>Recommended next steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>hrHPV+</td>
<td>HPV-16/18+ → Colposcopy HPV-16/18- → Cytology Abnormal → Colposcopy Normal → Retest in 1 y³</td>
</tr>
</tbody>
</table>

Sawaya GF, JAMA 2019
Co-Testing

The Future

- Cervical cancer (and its precursors) will become less common with more widespread HPV vaccination
- The greatest “bang for the buck” is achieved by screening all women for cervical cancer
- Cytology will be replaced with type-specific HPV screening
- Management of abnormal results based on an individual’s viral + risk profile and histopathology
  - Progression risk calculators will replace cytology based algorithms

Sawaya GF, JAMA 2019
The Evolving Screening Pelvic Examination Debate

The SPE Debate: Terms

- **Screening Pelvic Exam (SPE)**
  - External inspection, speculum and bimanual exam at the time of a WWV in an asymptomatic patient

- **Diagnostic Pelvic Exam**
  - Pelvic exam for the purpose of evaluating symptoms, signs, or other abnormal findings (lab, imaging)

- **Cervical cytology sampling**
  - Speculum used for the purpose cervical sampling
SPE: What’s the Fuss About?

Potential benefits

• Find an asymptomatic condition that is a health risk
  – Ovarian cancer
  – Benign neoplasm that could torse
• Find a symptomatic condition that the patient is unwilling to disclose or does not recognize as a problem
  – Urinary incontinence, pelvic organ prolapse
  – Sexual issues (GSM?)
  – HSIL of the vulva (VIN)

Ovarian Cancer Screening

February 2018

• Recommends against screening for ovarian cancer in asymptomatic women  Grade [D]
• Applies to asymptomatic women who are not known to have a high-risk hereditary cancer syndrome
### Other Potential Benefits: What Does the Evidence Say?

- Asymptomatic BV: not recommended CDC
- Asymptomatic trichomoniasis: targeted screening only
- VIN/vulvar cancer: no studies
- Fibroids: no studies
- Urinary incontinence: determine by history
- GU syndrome of menopause: determine by history

---

### SPE: American College of Physicians


- ACP recommends *against* performing SPE in asymptomatic, non-pregnant adult women
- Many clinicians include SPE as part of the WWV, and because it is *low-value care*, it should be omitted
Why Recommend Against SPE?

- Accuracy for detecting ovarian cancer is low
  - PLCO Trial: Ovarian cancer screening with ultrasound, CA-125, SPE: more harms than benefits
- No studies have assessed benefit for other conditions (PID, benign conditions, or other gyn cancers)
- Outcomes are not improved
- Harms: unnecessary laparoscopies or laparotomies, fear, anxiety, embarrassment, pain, discomfort
- Adds unnecessary costs

ACOG Well Woman Task Force
Obstet Gynecol 2015;126:697–701

For women age 21 years and older (Qualified)

- External exam may be performed annually
- Inclusion of speculum exam, bimanual exam, or both, in otherwise healthy women should be a shared, informed decision between patient and provider

“Qualified” recommendations rely primarily on expert consensus
Screening Pelvic Exam

- [ I ] Recommendation
- Current evidence is insufficient to assess the balance of benefits and harms of performing SPE
- “…clinicians are encouraged to consider risk factors for various gynecologic conditions and the patient’s values and preferences, and engage in shared decision making to determine whether to perform a pelvic exam”

The Utility of and Indications for Routine Pelvic Examination

- ObGyns and other providers should counsel asymptomatic women about the benefits, harms, and lack of data
- After reviewing risks and benefits, SPE may be performed if a woman expresses a preference for it
- Regardless of whether SPE is performed, a woman should see her ObGyn at least once a year for well-woman care
Should I Do a Screening Pelvic Exam...

- **ACP, AAFP (2014):** We know...don’t do it
- **ACOG (2015):** We think we know....do it. But discuss it first
- **USPSTF (2017):** We don’t know, but you may want to discuss it
- **ACOG (2018):** We don’t know, but you should discuss it

SPE: What Do We Tell Patients?

**Active**
- “3 national guidelines: each one is different”
- All 3 agree that there is no evidence of benefit
- Evidence of harms: “false alarms” and complications

**Passive**
- It is reasonable to say nothing about the SPE, and only respond to questions or to a request for an exam
How Can My Practice Prepare?

• Ask every patient if she sees a PCP/women’s HC provider
• Determine the screening policies for your practice
  – Seek consistency among your providers
  – Make sure that all staff are aware of your policy
• Inform your patients of changes that apply to them
  – During transition, leave decisions to patient
  – Inform patients with a personal letter or newsletter
• Keep track of benefit changes made by your payers
  – Few have changed screening benefits yet

The Well Woman Visit: Take It Home

• WWV shifted from exam room to consultation room
  – Less physical assessment, more counseling
• Shared decision making is more prominent
  – Reproductive intentions discussions
  – Family planning method discussions
  – Screening breast and pelvic exam
  – Age to begin mammography
There’s An App for That!

ARHQ
ePSS
Electronic Preventive Services Selector
References


References

References


References

References


• Sawaya GF. Screening Pelvic examinations: the emperor’s new clothes, now in 3 sizes? JAMA Intern Med 2017; 177:467–46
Management of Lipid Disorders

MANAGEMENT OF LIPID DISORDERS: Integrating the New Guidelines

Robert B. Baron, MD MS
Professor and Associate Dean
UCSF School of Medicine

baron@medicine.ucsf.edu

Disclosure

No relevant financial relationships
EXPLAINING THE DECREASE IN DEATHS FROM CVD

1980 to 2000: death rate fell by approximately 50% in both women and men

2000 to 2010: Death still falling: down 31%

- About 1/2 from acute treatments, 1/2 from risk factor modification:
  - Predominantly cholesterol, BP, smoking

Placebo-Controlled Statin Trials

Reductions in Major Coronary Events Relative to Placebo

- 38%
- 25%
- 25%
- 27%
- 31%
- 38%

simvastatin 20-40 mg  pravastatin 40 mg  pravastatin 40 mg  simvastatin 40 mg  pravastatin 40 mg  lovastatin 80 mg
Management of Lipid Disorders

Heart Protection Study: Vascular Events by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline Feature</th>
<th>Statin (10,269)</th>
<th>Placebo (10,267)</th>
<th>Risk Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td></td>
<td></td>
<td>Statin better worse</td>
</tr>
<tr>
<td>&lt;100</td>
<td>285</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>≥100 &lt;130</td>
<td>670</td>
<td>881</td>
<td></td>
</tr>
<tr>
<td>≥130</td>
<td>1087</td>
<td>1365</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td>24% reduction (p&lt;0.00001)</td>
</tr>
</tbody>
</table>

A RISK-BASED APPROACH

The benefit from any given intervention is a function of:
1) The relative risk reduction conferred by the intervention, and
2) The native risk of the patient
Management of Lipid Disorders

2013 ACC/AHA Guidelines

- Based only on RCT data
- Healthy lifestyle for all
- 4 groups of patients who benefit from statins
- Identifies high and moderate intensity statins
- No LDL treatment targets
- Non-statin therapies do not provide acceptable risk reduction
- Estimate 10-year ASCVD risk with new equation

2018 ACC/AHA Guidelines

- Based on RCT data plus other lines of evidence
- Healthy lifestyle for all
- 4 groups of patients who benefit from statins
- Identifies high, moderate and low intensity statins
- Some LDL treatment targets
- Non-statin therapies do provide acceptable risk reduction in some patients
- Estimate 10-year ASCVD risk with same equation
Management of Lipid Disorders

2013 and 2018 ACC/AHA Guidelines
Four Groups of Patients Who Benefit From Statins

- Individuals with clinical ASCVD
- Individuals with primary elevations of LDL ≥ 190
- Individuals age 40-75 with diabetes and LDL ≥ 70
- Individuals without ASCVD or diabetes, age 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher

2013 and 2018 ACC/AHA Guidelines
Importance of Lifestyle Recommendations

- Heart healthy diet
- Regular aerobic exercise
- Desirable body weight
- Avoidance of tobacco
**2013 ACC/AHA Guidelines**
**What Statin for Each Group?**

- **Individuals with clinical ASCVD:**
  - Treat with: high intensity statin, or moderate intensity statin if > age 75

---

**2018 ACC/AHA Guidelines**
**What Approach for Each Group?**

- **Individuals with clinical ASCVD:**
  - Treat with: high intensity statin, or maximally tolerated statin
  - Reduce LDL by 50%
  - In very high risk ASCVD (multiple events, major event and other risks), use 70 mg/dl to consider adding non-statins (ezetemibe and PCSK inhibitor)
2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals with primary elevations of LDL ≥190:
  - Treat with: high intensity statin

2018 ACC/AHA Guidelines
What Approach for Each Group?

- Individuals with primary elevations of LDL ≥190:
  - Treat with: high intensity statin
  - If over LDL >100, consider ezetemibe or PCSK9
Management of Lipid Disorders

2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals 40-75 with diabetes and LDL ≥ 70:
  - Treat with: moderate intensity statin, or high intensity statin if risk over 7.5%

2018 ACC/AHA Guidelines
What Approach for Each Group?

- Individuals 40-75 with diabetes and LDL ≥ 70:
  - Treat with: moderate intensity statin
  - If multiple risk factors or 50 - 75 years old use high intensity statin to reduce LDL by 50%
2013 ACC/AHA Guidelines
What Statin for Each Group?

- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - Treat with: moderate-to-high intensity statin

2018 ACC/AHA Guidelines
What Approach for Each Group?

- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - Have a clinician-patient risk discussion before starting statins
  - Risk factors, risk enhancing factors, potential benefits and harms, costs, and patient preferences and values (shared decision-making)
**2018 ACC/AHA Guidelines**

What Approach for Each Group?

- Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  - At 10-year risk of 7.5%, start a moderate intensity statin (if discussion favors statin)
  - Reduce LDL by 30% (or 50% if >20% ASCVD risk)
  - Risk enhancing factors favor statin
  - If risk uncertain, consider using coronary artery calcium

**2018 ACC/AHA Guidelines**

Risk Enhancing Factors That Favor Statin

- Family history
- LDL ≥ 160
- Metabolic syndrome
- Chronic kidney disease
- Hx of preeclampsia or premature menopause
- Chronic inflammatory disorders (RA, HIV, psoriasis)
- High risk ethnic groups (South Asian)
- Elevated triglycerides ≥ 175
- ApoB, hsCRP, ABI, lp(a)
2018 ACC/AHA Guidelines
Coronary Artery Calcium
• Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 7.5% or higher:
  • If risk uncertain consider CAC
  • Score 0: withhold treatment
  • Score 1-99: favors statin
  • Score >100: statin indicated

2018 ACC/AHA Guidelines
Borderline Risk
• Individuals without ASCVD or diabetes, 40-75, with LDL ≥ 70, and 10 year risk 5.0 - 7.5% or higher:
  • Risk enhancing factors may favor statin
Management of Lipid Disorders

2013 and 2018 ACC/AHA Guidelines
High Intensity vs. Moderate Intensity Statin

- High Intensity: lowers LDL by >50%
  - Atorvastatin 40 - 80
  - Rosuvastatin 20 - 40
- Moderate Intensity: lowers LDL by 30-50%
  - Atorvastatin 10 - 20
  - Rosuvastatin 5 – 10
  - Simvastatin 20 - 40
  - Pravastatin 40 – 80
  - Lovastatin 40

Pooled Cohort Risk Assessment Equations

- Age
- Gender
- Race (White/African American)
- Total cholesterol (170 mg/dl)
- HDL cholesterol (50 mg/dl)
- Systolic BP (110 mmHg)
- Yes/no meds for BP
- Yes/no DM
- Yes/no cigs
- Outcome: 10-year risk of total CVD (fatal and non-fatal MI and stroke)
Do the Pooled Cohort Risk Assessment Equations Overestimate Risk?

Percent of U.S. Adults Who Would Be Eligible for Statin Therapy for Primary Prevention, According to Set of Guidelines and Age Group.

How Best To Do Shared Decision Making?

Mayo Clinic Statin Choice Decision Aid:

- http://statindecisionaid.mayoclinic.org/index.php/statin/index?PHPSESSID=0khk8nm14h9vubjm3423e6h6b2
Other Lipid-Lowering Drugs

- Statins are treatment of first choice based on RCTs

- No evidence to support adding niacin or fibrates to statins

- Niacin has harmful affects in combination with statins and uncertain benefits when used alone (weak evidence)

- Fibrates appear to lower MI risk, but no other CVD endpoints.

Other Lipid-Lowering Drugs

- Ezetimibe study: (IMPROVE-IT)

18,000 ACS patients (40% from North America)

RCT: Simvastatin vs simvastatin + ezetimibe. Took 7 years. Death, MI, Stroke

Simvastatin: 34.7% vs Simva/ezetimibe 32.7% (270 fewer events over 7 years)
**PCSK9 Inhibitors**

- Evolocumab (Repatha) and alirocumab (Praluent)—monoclonal antibodies that reduce liver LDL-receptor degradation

- Reduce LDL by 50%. Injectable Q2 – 4 weeks

- Approved for FH or patients with CVD “who need additional LDL lowering.”

---

**FOURIER TRIAL**

- 27,564 patients, CV disease, on statin, LDL >70, 2.2 years

- Evolocumab vs placebo (SQ injections)

- Primary composite CV endpoint: death, MI, stroke, ACS revascularization

- Secondary endpoint: CV death, MI, stroke

Sabatine MS, NEJM, 2017
FOURIER TRIAL

• LDL reduced 59% (92 mg/dl to 30)

• Primary composite endpoint:
  • 1344 (9.8%) vs 1563 (11.3%)
  • 15% reduction

• Secondary endpoint: CV death, MI, stroke
  • 816 (5.9%) vs 1013 (7.4%)
  • 20% reduction

Sabatine MS, NEJM, 2017

FOURIER TRIAL

• NNT 66 over 2 years
• No reduction in death
• No obvious safety concerns

• Reflections:
  • Evolocumab reduces risk
  • Risk reduction less than hoped/thought
  • $14,000 per year

Sabatine MS, NEJM, 2017
ODYSSEY Outcomes

- 18,924 patients, ACS in last 12 months, on statin, LDL >70, 2.8 years
- Alirocumab vs placebo (SQ injections Q 2 weeks)
- Primary composite CV endpoint: CHD death, MI, unstable angina, or stroke
- Secondary endpoint: CHD death, CV death, MI, stroke

ACC, 2018

ODYSSEY Outcomes

- LDL reduced 55% (101 mg/dl to 53)
- Primary composite endpoint:
  - 9.5% vs 11.1%
  - 14% reduction
- Secondary endpoints:
  - All cause mortality: 3.5% vs 4.1% (15% reduction)
  - CHD Death: NS
  - CV death: NS

ACC, 2018
**PCSK9 Inhibitors 2018 Value Statement**

- “May be considered”
- Long-term safety (>3 years) is uncertain
- Economic value low is low at current prices

**CV Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia: REDUCE-IT**

- 8179 patients, hi risk (70% secondary prevention), on statin, TG >135 – 499
- Icosapent ethyl vs placebo (2g BID), 4.9 years, modest reduction in TG (14 mg/dl)
- Primary composite endpoint: CVD death, MI, stroke, unstable angina, or revascularization
- Secondary endpoint: CV death, MI, stroke

*NEJM, 2019*
Management of Lipid Disorders

**CV Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia: REDUCE-IT**

- Primary: 17.2% vs 22.0% (HR 0.75)
- Secondary: 11.2% vs 14.8% (HR 0.74)
- More atrial fibrillation and bleeding in Rx group
- Note: Icosapent ethyl ≠ omega 3 fatty acid supplements

NEJM, 2019

---

**Final Thoughts**

- Statins are effective and cost effective in selected groups of patients
- Use statins in patients with ASCVD, LDL ≥190 and diabetes
- Use statins for most patients with risk ≥20%
Final Thoughts

- For those without ASCVD, diabetes or LDL ≥190, calculate 10-year risk and treat those interested (shared decision-making)

- For patients with 5% - 20 % risk, enhancing factors may help decide

- In very high risk ASCVD patients, consider second medication (ezetimibe or PCSK9 inhibitor)

Final Thoughts

- Need more data on icosapent Ethyl
OUTPATIENT MANAGEMENT OF CAD- A PRIMARY CARE PERSPECTIVE

Michael G. Shlipak, MD, MPH
Scientific Director, Kidney Health Research Collaborative
Professor of Medicine, Epidemiology & Biostatistics
University of California, San Francisco
Associate Chief of Medicine for Research Development
San Francisco VA Medical Center
August 5, 2019

DISCLOSURES

I am on the Scientific Advisory Boards with stock option compensation for the following companies:

- TAI Diagnostics
- Cricket Health, Inc.
FEATURES OF THIS TALK

- Covers a broad array of topics
- Greatest attention to common challenges in decision making
- All recommendations supported by the following Guideline: *AHA Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease* (*Circulation, 2012*)
  - Class 1 indication: we should do this
  - Class 2 indication: it’s reasonable to do this

QUESTION #1

Your patient is a 62yo man with history of controlled hypertension, mild overweight (BMI 29), and untreated LDL of 137mg/dL. He reports to you that for about 2 months he has experienced left-sided chest tightness after working up 2 flights of stairs. It is relieved by rest and is not progressing noticeably. The symptoms have not occurred at any other times. **What is the probability that the patient’s symptoms are caused by CAD?**

a) <50%  
b) 60%  
c) 80%  
d) >90%
PRETEST PROBABILITY OF CORONARY HEART DISEASE IN PATIENTS WITH CHEST PAIN ACCORDING TO AGE, GENDER, AND SYMPTOMS

<table>
<thead>
<tr>
<th>Age</th>
<th>Nonanginal Chest Pain</th>
<th>Atypical angina</th>
<th>Typical angina</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30-39</td>
<td>4</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>40-49</td>
<td>13</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>50-59</td>
<td>20</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>60-69</td>
<td>27</td>
<td>14</td>
<td>72</td>
</tr>
</tbody>
</table>

AHA definitions: low risk ~10% or less, high risk ~90% or higher, intermediate risk- anything in between

Diamond GA et al., N Engl J Med 1979
Weiner DA et al., N Engl J Med 1979

QUESTION #2: YOUR PATIENT IS CAPABLE OF WALKING AND HAS A NORMAL RESTING ECG. WHICH OF THE FOLLOWING TESTS SHOULD YOU ORDER NEXT?

a) Exercise only stress test
b) Exercise with perfusion imaging
c) Exercise echo
d) Coronary angiography
e) None of the above
NON INVASIVE TESTING FOR DIAGNOSIS OF ISCHEMIC HEART DISEASE

AHA recommendation is to limit testing to intermediate risk patients

- If patient can exercise and has normal resting ECG, then exercise only stress test
- If abnormal ECG, then exercise/imaging or exercise echo
- If patient cannot exercise, then pharmacologic stress with imaging/echo

WHY DO WE ONLY TEST PATIENTS WITH INTERMEDIATE PROBABILITY OF CAD?

- Exercise only:
  - \( LR^+ = 3.0 \)
  - \( LR^- = 0.42 \)

- Exercise echo:
  - \( LR^+ = 3.7 \)
  - \( LR^- = 0.19 \)
  (Fleischmann KE. et al. JAMA 1998)

- Exercise imaging:
  - \( LR^+ = 2.4 \)
  - \( LR^- = 0.20 \)
  (Fleischmann KE. et al. JAMA 1998)
PROMISE TRIAL

Is coronary CT angio the best tests for evaluation of intermediate risk patients with chest pain?


TRIAL DESIGN

- 10,000 participants in North America
- 193 sites
- NIH-funded
- Randomization:
  - CTA- coronary computed tomographic angiography
  - Functional Testing- (one of the 3 options)
    - Exercise EGG
    - Nuclear stress
    - Stress echo
  - Composite: death, MI, UA hospital procedure complication
- Median follow-up 25 months
PATIENT CHARACTERISTICS

- Age: 60±8
- Women: 53%
- Mean: 2.4 risk factors
- Typical angina: 17%
- Atypical angina: 78%
- Non-anginal symptoms: 10%
- Individual predicted CAD risk: mean 0.53

QUESTION 3

Among these intermediate risk patients, what percentage would you guess had the primary outcome (death or MI) within 2 years?

a) <5%
b) 5-10%
c) 10-20%
d) >20%
CT ANGIO IS NO BETTER THAN FUNCTIONAL TESTING

Incidence of death or MI was only 1%/year in each group

SUMMARY

- A lot of testing with very low yield
- “Intermediate risk” is actually low risk
- “...reflects an excellent prognosis for patients with similar, new-onset, stable chest pain in real-world settings.”
QUESTION #4

Based on his symptoms of typical angina, you inform your patient that he has CAD. You explain the proven value of “optimal medical therapy”

Which of the following is not considered part of optimal medical therapy for a patient with anginal symptoms?

a) ACE inhibitors (ARBs)  
b) Aspirin  
c) Beta blockers  
d) Statins

ASPIRIN

- All patients with CAD should use 81-162mg of aspirin (class 1)  
- Clopidigrel (plavix) should be offered to patients who cannot tolerate aspirin (class 1)  
- Aspirin + clopidigrel for severe patients is reasonable (class 2B)
**Beta Blockers**
- Improved survival in patients with prior MI
  - If patient has prior MI, BB is class 1
  - If MI >3 years ago, BB is class 2A
- Best choice for angina symptoms

**Statins (More on this topic later)**
- LDL target <100 mg/dL - class 1
- LDL target <70 mg/dL - class 2A
- “No evidence to suggest LDL targets of 70 vs. 100mg/dL in patients with ASCVD”
ACE INHIBITORS

- Not clearly indicated in patients with angina because no effect on symptoms
- Considered a “reasonable choice” (2A)
- ACE inhibitors (Class I) must be used for patients with:
  - Reduced ejection fraction
  - CKD with albuminuria

CASE CONTINUED

- Your patient worries that something bad might happen with his heart. He asks you to assess the likelihood of him having a heart attack or dying from his heart disease. How do you determine risk in the secondary prevention setting?
RISK PREDICTION IN CAD

- **Primary prevention:**
  - Patients without CAD or CVD
  - CVD risk calculator

- **Secondary prevention:**
  - Patients who have CAD
  - No risk score for ambulatory patients with established CAD
  - CVD risk calculators do not work

RISK FACTORS FOR ADVERSE OUTCOMES IN PATIENTS WITH CAD

- Feared adverse outcomes in CAD patients:
  - Recurrent MI
  - Heart failure
  - Sudden death

- Traditional CVD risk factors are still important:
  - Blood pressure control
  - Smoking cessation
  - Weight loss
  - Diabetes control
  - Lipid management
  - Encourage exercise

- Although important, cardiac status matters more for prognosis than metabolic risk factors
CARDIAC-SPECIFIC RISK FACTORS IN PATIENTS WITH CAD

1. Exercise capacity
2. Number and size of MIs
3. Reduced ejection fraction
4. HF symptoms
5. BNP/NT-pro-BNP
6. High sensitivity troponins

TREATMENT OF ANGINAL SYMPTOMS

RANKING ANTI-ISCHEMIC AGENTS (PER AHA GUIDELINES)

1. BBs- top choice
2. CCBs or long acting nitrates (if BB intolerant)
3. Use combinations if necessary
4. NTG (sl or spray) for immediate relief
5. Ranolozine as lesser alternative (class 2A)
**FOLLOW UP IN CAD PATIENTS**

**Routine**
- Assess anginal symptoms and physical function
- Assess signs of heart failure or arrhythmia
- Risk factor management
- Lifestyle

**Situational**
- If heart failure signs or repeat MI → echo
- If new or worsening angina → *exercise testing* or coronary angiography

---

**CASE STUDY FOLLOW UP**

- Your patient is still frustrated by the concept of medical management and concerned that his symptoms indicate an impending heart attack. He asks you “why can’t I just get a stent and fix this problem?”

  **This seems logical- why not proceed to PCI?**
INTERVENTIONS IN STABLE ANGINA

- Interventions should be limited to patients who fail optimal medical therapy
- Currently, 85% of all percutaneous coronary intervention (PCI) procedures are elective in patients with stable angina
- The COURAGE trial demonstrated that PCI does not improve outcomes

COURAGE TRIAL

- Conducted to compare OMT with and without PCI in 2,287 patients with stable angina
- Funded by the US VA R&D/Canadian Institutes of Health Research
- Outcome:
  - All-cause mortality
  - Non-fatal MI
- Initial trial: mean of 4.6 years
  - Boden et al. NEJM 2007
- Extended follow-up: 12 years
  - Sedlis et al. NEJM 2015
**CASE STUDY FOLLOW UP**

- Your patient insists on talking with a specialist
- You refer to a cardiologist
- The patient returns to your office 8 weeks later for a follow-up visit...

...after having received a stent.

**What happened?**
What are cardiologists thinking?

CARDIOLOGISTS’ USE OF PCI FOR STABLE CAD

- **Design**: focus groups of cardiologists in N. Cal
- **Research Question**: Why do cardiologists ignore COURAGE results?
- Reasons given for performing PCI in stable angina:
  - Belief in the benefits of treating ischemia and in the open artery hypothesis
  - Potential regret (psychological and legal) for not intervening if a cardiac event could be averted
  - Alleviation of patient anxiety
  - Belief that referring PCP expects a procedure

Lin et al. Arch Intern Med. 2007
WHY STATINS ARE BETTER THAN STENTS

- Severity of stenosis ≠ MI risk
- Stents are small (1-2 cm) relative to length of 3 major coronary arteries (~30 cm) and their branches (>30 cm)
- Statins stabilize all the plaques

CONCLUSIONS

- We need to fully implement OMT (β-blocker, statin, aspirin) first, before referring to cardiologists
- We need to resist the urge to “fix” patients’ angina by stenting
- We need to educate patients that stents do not prevent adverse outcomes
- We need to be clear about our expectations prior to referring patients to cardiologists
**QUESTION 5**

- Your patient returns for follow up. He has been taking 20mg simvastatin. LDL is 110mg, HDL 25mg. Which is the best next step?
  - a) ↑ simvastatin
  - b) Change to pravastatin
  - c) Change to atorvastatin
  - d) Add gemfibrozil
  - e) Add niacin

**NEW RECOMMENDATIONS FOR LIPID MANAGEMENT IN PERSONS WITH CVD**

- “High intensity statin therapy should be first line in persons with clinical ASCVD, aged ≤ 75, unless contraindicated”
  - **High**- atorvastatin 40-80, rosuvastatin 20-40
  - **Moderate**- simvastatin 20-40, pravastatin 40, lovastatin 40
  - **Low**- simvastatin 10, pravastatin 10-20, lovastatin 20
- **Our patient should be on atorvastatin or rosuvastatin**
SHOULD WE STILL USE SIMVASTATIN?

- June 8, 2011: FDA restricts use of 80mg simvastatin because of increased risk of myopathy
- FDA recommends:
  - No new patients on simvastatin 80mg
  - Okay to maintain patients on 80mg if >1 year without symptoms of muscle toxicity
  - Beware of drug interactions
- Based on the SEARCH Trial (Lancet, 2010)
  - Simvastatin 80mg vs. 20mg in RCT of 12,000 with CAD

SEARCH TRIAL RESULTS

- Difference in myopathy risk:
  - **Myopathy** (muscle weakness + CK >10x ULN)
    - 80 mg: 52 patients (0.9%)
    - 20 mg: 1 patient (0.02%)
  - **Rhabdomyolysis** (muscle weakness + CK>40x ULN)
    - 80 mg: 22 patients (0.4%)
    - 20 mg: 0 patients
- Risk 5-fold higher in year 1 compared with subsequent years
- Key drug interactions noted
  - Calcium channel blockers, Amiodarone, Ranolazine, and others

SEARCH Study Group *The Lancet*, 2010
**QUESTION 6**

You decide your patient should switch to atorvastatin. However, he has now stopped his statin due to adverse publicity and will not restart. He tells you that he is now taking niacin because it is “a natural option.”

You recheck his lipids; his HDL is 50mg/dL and his LDL is 140 mg/dL.

**Your best management option is:**

a) Reinforce to the patient that statins are by far the best treatment for lipid disorders.

b) Congratulate him on his choice because niacin has made his HDL go up beautifully

c) Offer a fibrate (e.g. gemfibrozil), as it is an evidence-based treatment for patients like him

d) Any of the above approaches is fine.

---

**WHY IS NIACIN IN DISFAVOR?**

- **AIM-HIGH trial** *(NEJM 2011)*
  
  AIM-HIGH Investigators, *NEJM* 2011

- **HPS2-THRIVE trial** *(NEJM, July 17, 2014)*
  
  [http://www.ctsu.ox.ac.uk/hps2-thrive/](http://www.ctsu.ox.ac.uk/hps2-thrive/)
  HPS2-THRIVE Investigators, *NEJM* 2014
AIM-HIGH TRIAL (NIH, ABBVIE)

- **Participants**: N=3,414 in US and Canada
- **Inclusion criteria**:
  - Prior CVD
  - On a statin
  - Low HDL and high TG
- **Design**: Placebo-controlled RCT
- **Intervention**: Niaspan – 2 g/day or placebo
- **Outcomes**: CVD death, MI, CVA, ACS, revascularization
- **Follow-up**: 3 years

http://www.aimhigh-heart.com/
AIM-HIGH Investigators, *NEJM* 2011

AIM-HIGH FINDINGS

- Trial stopped early
- Event rate was same in both groups

http://www.aimhigh-heart.com/
AIM-HIGH Investigators, *NEJM* 2011
HPS2-THRIVE TRIAL (MERCK)

- **Participants**: N=25,673 in UK, Scandinavia, and China
- **Inclusion criteria**:
  - Prior CVD
  - On a statin
- **Design**: Placebo-controlled RCT
- **Intervention**: 2g ext-release niacin + 40mg laropiprant vs. placebo
- **Outcomes**: CVD death, MI, CVA, and revascularization
- **Follow-up**: 4 years

http://www.ctsu.ox.ac.uk/hps2-thrive/
HPS2-THRIVE Investigators, NEJM 2014

HPS2-THRIVE FINDINGS

- Primary outcome RR= 0.96 (0.90-1.03)
- All-cause mortality RR= 1.09 (0.99 to 1.21)

http://www.ctsu.ox.ac.uk/hps2-thrive/
HPS2-THRIVE Investigators, NEJM 2014

But, there is more to the story…
# Niacin Increases Risk for Serious Adverse Events and Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate Ratio (95% CI)</th>
<th>Extra Events/100 Users</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Event</td>
<td>1.28 (1.13-1.44)</td>
<td>1.0</td>
</tr>
<tr>
<td>Musculoskeletal event</td>
<td>1.26 (1.10-1.44)</td>
<td>0.7</td>
</tr>
<tr>
<td>Skin-related event</td>
<td>1.67 (1.20-2.34)</td>
<td>0.3</td>
</tr>
<tr>
<td>Infection event</td>
<td>1.22 (1.12-1.34)</td>
<td>1.4</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>1.38 (1.17-1.62)</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New-onset</td>
<td>1.32 (1.16-1.51)</td>
<td>1.3</td>
</tr>
<tr>
<td>Worsened condition</td>
<td>1.55 (1.34-1.78)</td>
<td>3.7</td>
</tr>
</tbody>
</table>

http://www.ctsu.ox.ac.uk/hps2-thrive
HPS2-THRIVE Investigators, NEJM 2014

- “On the basis of the weight of available evidence showing net clinical harm, niacin must be considered to have an unacceptable toxicity profile for the majority of patients, and it should not be used routinely.”
- “...[the study] lends further evidence to the notion that HDL cholesterol is unlikely to be causal.”
Do fibrates improve clinical outcomes?

**Effects of Fibrates on Cardiovascular Outcomes**

- **Design:** systematic review and meta-analysis
- **Analysis:** 18 RCTs from 1950-2010
- **Participants:** N=45,058

Jun et al. *The Lancet* 2010
FIBRATE VS. PLACEBO AND CVD RISK

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>1.00</td>
<td>0.98-1.08</td>
<td>0.92</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.97</td>
<td>0.88-1.07</td>
<td>0.59</td>
</tr>
<tr>
<td>Total stroke</td>
<td>1.03</td>
<td>0.91-1.16</td>
<td>0.69</td>
</tr>
<tr>
<td>Non-fatal coronary events</td>
<td>0.81</td>
<td>0.75-0.89</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Jun et al. The Lancet 2010

DATA SUMMARY

- **For patients with low HDL:**
  - Statins are treatment of choice to decrease CVD risk, regardless of LDL
  - Do not add either niacin or fibrates to statin treatment

- **For patients who cannot tolerate statins:**
  - Fibrates appear to lower MI risk, but no other CVD endpoints
  - Niacin has clear harmful effects and uncertain benefits among statin non-users.
  - AHA guidelines state that for statin untreated patients fibrates are a “reasonable choice” (2A)
CASE STUDY FOLLOW UP

- Now that your patient with stable CAD is on OMT, he has increased exercise, as you recommended.
- However, he has developed persistent knee pain and wants to take “prescription-strength” ibuprofen. The label says to ask a doctor before use if you have heart disease.
- Is the risk real?

NSAIDS IN CAD PATIENTS

- Meta-analysis demonstrated increased risk for incident CAD (Trelle et al. BMJ 2011)
- Are they clinically harmful in patients with established CAD?
- No RCT evidence in CAD patients
BEST EVIDENCE FROM DENMARK

- National registry of MI patients and pharmacy data
- Patients with first MI (2002-2011); N= 61,971
- 34% received NSAIDS; average age = 68, 63% men
- Follow-up for MI/CHD death
- Follow-up for bleeding risk

Olsen AM et al. JAMA 2015

NSAID ASSOCIATION WITH CVD RISK

- Outcome: CVD death, MI, stroke
- No NSAID: 8.3%/year
- NSAID: 11.2%
- Adjusted HR: 1.40 (1.3-1.5)
- Risks similar across NSAIDS; naproxen rarely used

Olsen AM et al. JAMA 2015
NSAID ASSOCIATION WITH BLEEDING RISK

- Outcome: Intra-cranial, GI, respiratory, or urinary bleeding
- No NSAID: 2.2%/year
- NSAID: 4.2%
- Adjusted HR: 2.0 (1.8-2.3)
- Risks similar across NSAIDS

Olsen AM et al. JAMA 2015

NSAID CONCLUSIONS

- MI risk from NSAIDs appears real
- NSAIDs should be used at most for short-term in CAD patients
- Evidence supports FDA’s “Black Box” warning (FDA update 7-9-2015):
  - NSAIDs cause MI and stroke, even in first weeks
  - Increased risk with higher dose and duration
  - Uncertain whether risk varies by particular NSAID
  - NSAIDs also cause HF
THANK you!
ANY QUESTIONS?
What the primary care provider needs to know

Toby Maurer, MD

Objectives

• Review most common diseases in dermatology
• Strengthen the partnership between the PCP and derm to provide the best care to the pt?
Acne

Primary care provider:
Pt has recent onset of bumps on face. What is this and how do I treat? Has used “proactive “with minimal change.

Topicals

• BP 5% gel (10% - more drying)
• Retin A 0.025% - 0.1% (vehicle determines strength - start with crème)
• Cleocin T or erythromycin topically
  — Use 1 qam and 1qhs
  — If NO success after 8 weeks, go to p.o.’s
Primary Care Provider:

Pt with acne – used Retin-A but very irritating. What is the next step?

- Pt has cystic/scarring acne-topicals won’t work and in Asians-Retin A is very irritating.
- Start p.o. antibiotics
- Adapaline (topical) may help to shrink scars
P.O. Antibiotics

- TCN - 500 bid x 8 weeks
- Doxycycline - 100 bid x 8 weeks
- Minocycline - 100 bid x 8 weeks
- Taper - Do NOT STOP ABRUPTLY. Once pt’s skin is clear, taper the dose in ½ for another month and then stop the medication

Scarring, keloidal, cystic acne

- Record treatments
- If failed 2 or more systemic meds, consider Accutane
- Check depression history, CBC, LFT’s, TG, Chol and pregnancy counselling
Acne Rosacea

• Rosacea-if just red-laser or makeup
• If papules-start doxy 100 bid x 8 wks then topical flagyl daily for maintenance
• Seb derm: topical HC 1% oint plus econazole crème bid and seb derm shampoo (tar, ketoconazole, selenium, zinc)

Acne Keloidalis Nuchae

• Never buzz cut hair again
• Topical clobetasol qam and topical retin a 0.1% crème/gel qhs x 3 months
• If very inflamed, add doxycyline 100 bid x 2 months
• See pt back in 3 months
• If no change, send back another consult-we can book him in clinic for intralesional kenalog
• New association with metabolic syndrome (especially HTN)
• Primary Care Provider:
Pt told he has psoriasis-used some crème in Mexico-can’t remember name. Worried that his grandchildren could catch this.

• Psoriasis is fast growing skin-can’t get it from anyone and can’t give it to anyone
• What meds is he on? Certain meds might unmask this like atenolol, lithium, NSAIDS
• Start Clobetasol oint and dovonex crème together. Apply M-F bid-weekends off
• Primary see pt again in 6 weeks. If not better-send another telederm consult and we will readvise or book pt in derm clinic
Pt did not get better......

- New pictures show increased total body surface area involvement
- Dermatology triage: I see that pt has liver disease (seen on EMR). First choice systemic drug is acitretin. Please order up baseline LFT’s, fasting TG and cholesterol.
- We will book pt for derm clinic in 3 weeks- please order baseline labs and start him on acitretin 25 qd

Psoriasis-when topicals don’t work

- **Acitretin**-safer to use in liver disease-monitor TG, Chol
- **Methotrexate**-titrate dose, follow LFT’s and CBC, needs liver biopsy after 1.5 gm-great drug if there is psoriatic arthritis
- **Biologics**-good drugs, expensive, subcu injections except for ombrelilast, presecreen for TB and Hep B and cancer risk
- **Ultraviolet light**-is pt able to spend the time; is it accessible to pt?
Psoriasis and Metabolic Syndrome

- associated with HTN and cardiac disease
- associated with renal disease
- Chronic inflammation-no evidence that the TNF blockers or aictretin are helpful in down regulating systemic inflammatory markers
- Did not check against MTX

LOTS of BIOLOGICS

- Personalized medicine
- Starting to look at tissue flow cytometry to identify specific markers in an individual and then use the most specific targeted biologic
- Especially useful in pts who have failed multiple different biologics
Atopic Dermatitis Body Treatment

- Topical steroids and antihistamines still mainstay of treatment
- Avoid prednisone (oral and injectable)
- Clobetasol ointment qd for 5 days when severe then
- Fluocinonide (lidex) oint bid for 2 weeks then
- Triamcinolone 0.1 % oint bid maintenance
- FACE: HC or aclomethasone oint bid

Gentle Skin Care discussion

- Steroids are okay to use-not going to thin out the skin BUT give limited amts of potent steroids
- Use steroids with grease-bid when disease is active
- Otherwise JUST GREASE
- Bathing or showering 1-2x’/wk and don’t even dry off after bathing
- Grease up immediately
- Antihistamine (benadryl, atarax, doxepin) at night so pt can sleep and break the itch/scratch cycle
Dupilumab

- Anti-IL4 receptor
- Expensive
- SEVERE atopic derm

Scabies: Classic treatment

- Permethrin 5% crème-2 applications 1 week apart
- Must treat all intimates
- Clothing instructions essential-wash 3 days of clothing and linens, then apply permethrin-start using clean clothes next morning
- Everything else goes into garbage bags-tie off for 3 days
Primary Care Provider:
Pt notes changing mole—also itchy. Worried she has melanoma

- Seborrheic keratosis—OBSERVE over time—Alert to pt—if bleeds or grows rapidly—return to you ASAP!
- You can apply cryotherapy 2 x 15 sec thaw cycles or
- Private derms in your county will do this for a fee
• Primary Care Provider:
  24 year old with new black bump
• No others noted

• Pt notes these get caught on shirt-sometimes get inflamed
• Skin tags-benign
• Primary can snip them off-dermatologists not reimbursed for this

New red/brown bump
• Dermatofibroma-often on arms and legs of women
• Banal-reaction to bug bite or trauma
• Resolves in 20 yrs
• Don’t excise
• Primary Care Provider:
  30 yr old with multiple previous biopsies to rule out melanoma. Here for skin check.
• No recent changes in moles
• No family history of melanoma
• These pts should be seen at least once by dermatologist to determine risk for melanoma and plan for monitoring

Melanoma

• Melanoma may be INHERITED or occur SPORADICALLY
• 10% of melanomas are of the INHERITED type Familial Atypical Multiple Mole-Melanoma Syndrome (FAMMM)
Ask these questions:

1) Personal or family history of melanoma?
2) History of atypical nevus that has been removed?
3) Presence of new or changing mole- i.e. change in size or color?

Risk Factors for Sporadic (Nonhereditary) Melanoma

- Numerous normal nevi, some atypical nevi
- Sun sensitivity, excessive sun exposure
Clinical Features of FAMMM

- Often numerous nevi (30-100+)
- Nevi > 6mm in diameter
- New nevi appear throughout life (after age 30)
- Nevi in sun-protected areas (buttocks, breasts of females)
- Family history of atypical nevi and melanoma

Prevention

- Self examination/spousal exam for low-risk individuals
- Self examination/spousal exam and regular physician examination (yearly to every several years) for intermediate risk individuals
- Self examination and examination by a dermatologist every 3-12 months for FAMMM kindred
If not sure:

- Measure and see pt back in 3-6 months for reevaluation!!

Primary Care Provider:

On pts back-Sometimes wife squeezes out smelly cheese –like material. Advice?
• Epidermoid cyst-not inflamed. Does not need to be excised unless repeatedly inflamed.
• Wife should stop squeezing this-could cause cyst contents to be released into surrounding tissue-causing inflammation
• If pt wants this excised-please send to surgery for excision-may not be covered by insurance

• Primary Care Provider:
  Pt came in with 2 day history of enlarging lesion and increasing pain.
  • Started doxycyline
Inflamed Epidermoid Cysts

- Antibiotics-USELESS-this is abscessed-6 papers and metanalysis shows that antibiotics will not help where an I and D should be done
- If just starting to become inflamed and cyst is small ( < 1 cm), can try intralesional Kenalog injection but see them back in few days-you can exacerbate the inflammation
- This cyst is bigger than 1 cm
- INCISE and DRAIN and PACK-send to surgery or ER today
- 6 weeks later, inspect for residual cyst and send pt for excision to surgery

Keloids

- These are keloids
- Did they come from acne-if so-look for other acneiform lesions and let me know-I can discuss systemic acne treatment so that pt does not get new keloids after every acne breakout.
- Will need intralesional kenalog-will book with derm clinic for monthly injections-book within next two months
Vitiligo

- Immune system hyperactive
- Thyroid disease (19%) and other autoimmune diseases—screen for thyroid dz every 3 yrs
- Trial of clobetasol oint qd x 3 months; if not working tacrolimus bid x 3 months then leave it alone
- Makeup, counselling

Alopecia areata

- Non-scarring alopecia—we have no idea why it starts and we don’t have preventive treatment in terms of halting future episodes
- Inject with intralesional kenalog 10mg/cc q month for at least 6 months to see if there is hair regrowth
- For widespread areas: Trying to understand the immune pathway-opremilast and JAK inhibitors
• Pt has actinic keratosis
• Can I freeze it with liquid nitrogen?

• Yes-2 x 15 sec thaws –appropriate treatment. Please make sure that you have looked at all sun-exposed areas to rule out non-melanoma skin cancers
• ARE ANY SPOTS BLEEDING?
• Please explain side effects of LN2
• Please see pt back in 1 month-if lesion not resolved, please biopsy or send pt for biopsy to live derm clinic
I have no disclosures relevant to this talk

General Disclosures

• Bayer: litigation consultant
• Sebela Pharmaceuticals:
  – Investigator proctor in phase III trial of a copper IUD (VeraCept)
Routine Screening: Chlamydia and GC

- **USPSTF (2014)**
  - Annually for sexually active non-pregnant women ≤ 24 [B]
  - Older women who are at increased risk [B]
  - Men: [ I ] No recommendation
- **CA STD Control Branch**
  - If practice-site prevalence (PSP) is...
    - Chlamydia > 3%
    - Gonorrhea > 1%
Increased Risk for Ct/ GC

- Previous or concurrent STI
- New or multiple sex partners
- A sex partner with concurrent partners
- A sex partner with an STI
- Inconsistent condom use among persons who are not in mutually monogamous relationships
- Exchanging sex for money/drugs/safety/housing

Targeted Ct, GC Screening: Risk Factors

Ct and GC screening in women 25 years and older, and PSP is low (Ct is <3% and GC is <1%)
- History of GC, chlamydia, or PID in the past 2 years
- More than 1 sexual partner in the past year
- New sexual partner within 90 days
- Reason to believe that a sex partner has had other partners in the past year
- Sex in conjunction with drug use
NAAT Vaginal Swab Is Preferred Specimen Source

- Sensitivity is equal or greater to cervical swabs or urine
- Self-collection option well accepted women of all ages
- Less specimen processing than with urine
- Check with your lab regarding specimen handling
- Multi-site screening in MSM; no guidelines for females
  - Screen females based on sexual history...not routinely
  - NAAT test (and CPT code) same, regardless of site(s)

What About Rectal CT and GC in Women Seen in STD Clinics?

- Chandra et al, STI 2018
  - Rectal CT positivity overall: 6% (95% CI, 3.2-8.9%)
  - Rectal CT if reporting anal sex: 25.9% (95% CI 9-43)
  - Percentage of rectal infections that would be missed with only urogenital screening: 18-23%
  - Rectal GC: 1.9% ; pharyngeal GC: 2.1%
  - Rectal chlamydia: 8.7%; pharyngeal chlamydia: 1.7%
Let’s Talk About Technique

- Throat: Swab both tonsillar pillars (watch out for gagging)

- For rectal swab: Insert 3-4 cm and twirl the wrist 360°

GC/CT NAAT: Optimal Urine Specimen Collection

- 1st catch: don’t urinate an hour before providing specimen
  - If patient urinated < 1 hr before, ok to use specimen, but sensitivity may be reduced

- What if we only have a midstream urine?
  - 96/100 participants with first-void urine + for CT also had a positive midstream urine (CI 90-99%)
  - Ok to use specimen, but sensitivity slightly reduced

Mangin et al J Fam Pract 2012
Contact Testing for STI Exposure
aka: “Screen Me for Everything”

• Test asymptomatic persons with high risk sexual exposure (new or multiple sexual partners) for
  – Gonorrhea
  – Chlamydia
  – Syphilis
  – HIV
• Maybe: HSV-2 serology
• No contact testing for
  – HSV (culture), HPV (DNA)
  – HBC, HBV (strategy for HBV is vaccination)

Screening for Hepatitis B

• Have you previously been vaccinated for Hepatitis B?
  – Yes...no further evaluation
  – No...offer HBV vaccination if HB risk factors
  – Don’t know...check! If can’t find out, do serology
• If HB vaccine is offered, pre-vaccination HB serology
  – *Is not* cost effective in low prevalence groups,
  – *Is cost* effective in high prevalence adult populations
    • IDU, MSM, sexual contacts of chronic carriers, persons from endemic countries
  – If screened, give 1st dose of vaccine at same time
Screening for Hepatitis C

• Sexual transmission is very uncommon
• Candidates for targeted screening
  – Blood transfusion from a donor later positive for hep C
  – Injected illegal drugs, even if experimented a few times many years ago
  – Transfusion or organ transplant before 7/1992
  – Recipient of clotting factor(s) made before 1987
  – Ever been on long-term kidney dialysis
  – Evidence of liver disease (e.g., abnormal LFTs)

Recommendations for Identification of Chronic Hep C Virus Infection, Persons Born 1945–1965
MMWR 2012;61(RR04);1-18

• Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk, and
• All persons identified with HCV infection should receive a brief alcohol screening and intervention, followed by referral to appropriate care services for HCV infection
Treatment of GC + Chlamydia (Ct)

- Positive GC or Ct screening test
- Sexual partner with person with known GC or Ct
- Presumptive therapy of mucopurulent cervicitis or urethritis (treat both partners)
- Pelvic inflammatory disease (treat both partners)

Lower Genital Tract Chlamydia

- Preferred regimen
  - Azithromycin 1 gm orally, directly observed
    - First line treatment in pregnancy
  - Doxycycline 100 mg PO BID for 7 days
    - Avoid prolonged sun exposure (photosensitivity)
- Alternative regimen
  - Ofloxacin 300 mg PO BID for 7 days
  - Levofloxacin 500 mg PO QD for 7 days
  - Erythromycin base or EES QID for 7 days
- NOTE: Ciprofloxacin not effective!
Lower Genital Tract Chlamydia

*added in 2015*

**Alternative Regimen: Non-pregnant**
- Doxycycline (delayed release) 200 mg QD x 7 days
  - Equally efficacious to BID doxy, less GI side effects
  - More expensive

**Moved to Alternative Regimen: Pregnant**
- Amoxicillin 500 mg PO TID x 7 days

Anogenital Gonorrhea

**Recommended regimens**
- Ceftriaxone 250 mg IM + dual therapy

**Dual therapy drugs**
- Preferred: azithromycin 1 gram PO
- If azithromycin allergy, doxycycline 100 mg PO BID

**Why dual therapy??**
- Prevent (or delay) GC cephalosporin resistance
- Co-treat “for chlamydia”, even if NAAT is negative
- Preferably, simultaneously and direct observation
Anogenital Gonorrhea

Alternative cephalosporins
• Cefixime 400 mg orally once
  PLUS
• Dual treatment with azithromycin 1 gm PO or doxycycline 100 mg BID x 7 days, regardless of CT

In case of severe allergy
Gentamicin 240 mg IM + azithromycin 2 g PO
OR
Gemifloxacin 320 mg orally + azithromycin 2 g PO

Test of Cure After Ct or GC Treatment
• Not after high efficacy, single dose treatment
• Exceptions…perform test of cure
  – Pregnancy
  – Noncompliant with therapy
  – Persistent symptoms despite therapy
  – Suspect early reinfection after adequate therapy
  – Pharyngeal GC treated with an alternative regimen
  – Multi-day antibiotics with high failure rate
• Avoid non-culture tests within 3 weeks of treatment
Check List: Management of Ct and GC

☑ Ensure timely and appropriate treatment
  – Within 14 days of specimen collection
☑ Test for other STDs
  – GC, syphilis, HIV
☑ Patient education and counseling
☑ Report case to the local health department
☑ Schedule follow-up test in 3 months
☑ Ensure that sex partners are treated
  – All partners in the past 2 months

Ct & GC Screening Post-Treatment

• **Re-screening:** women treated for chlamydia, GC or trichomonas should be re-screened in 3 months
  – In young women, past infection is strong predictor of repeat infection
    • 20% will have a new infection(s) by an untreated partner or new partner within 12 months
  – Short time to repeat positive test
  – 4x risk of PID, 2x risk of ectopic pregnancy
Partner Management: WHO?

• Treat ALL sexual partners within 2 months of positive gonorrhea or chlamydia test
  – Ask how many people she has had sex with during the previous 2 months
  – Ask regardless of marital/relationship status
  – If last sexual contact was longer than 2 months ago, treat most recent partner

Partner Management: HOW?

• Traditional approaches
  – Patient notification of partner
  – Provider notification of partner
  – Health department referral
• Preferred approach
  – Expedited Partner Therapy (EPT)
    • 2015 CDC STD Treatment Guidelines
    • ACOG Committee Opinion #737, ObGyn, June 2018
Expedited Partner Treatment (EPT)

- **Bring Your Own Partner (“BYOP”)**
  - Bring her partner(s) at the time of her treatment

- **Patient-delivered partner therapy (“PDPT”)**
  1. Provide patient with drugs intended for partners
  2. Prescribe extra doses in the index patients’ name
  3. Write prescriptions in the partners’ names
    - Ideally with written instructions for the partner(s)

---

The Effectiveness of Expedited Partner Treatment (EPT) on Re-Infection Rates

<table>
<thead>
<tr>
<th>Condition</th>
<th>Usual Care</th>
<th>EPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GONORRHEA</strong></td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>CHLAMYDIA</strong></td>
<td>13%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Partner Management

• Clinical evaluation first-line option
• Concurrent patient-partner therapy (BYOP) may be effective for patients with one partner
• Offer PDPT routinely to heterosexual patients with CT/GC if partner cannot be promptly treated
  – Dual therapy (cefixime 400 mg + azithromycin 1 g) is crucial if PDPT is offered
HIV Screening

- Screen *all* individuals once between 15-65 years old [A]
- Repeat annually or more often if “known risk”
  - Sex partner with HIV, injection drug use, commercial sex work, a new sex partner (since a prior HIV test) whose HIV status is unknown, care at STD or TB, correctional facility, or homeless shelter
- Use 4th gen HIV test; positive result 4 weeks earlier than 3rd
  - HIV-1, HIV-2 antibodies
  - HIV-1 p24 antigen

Primary and Secondary Syphilis: Reported Cases, U.S., 1941–2017*

Primary and Secondary Syphilis Cases have increased 390% since 2001

CDC estimates more than 55,000 people are infected each year

Bolan, NRHC 2018
Congenital Syphilis (CS) Cases and Primary and Secondary (P&S) Syphilis Cases Among Females of Reproductive Age, U.S., 2007–2017*

![Graph](image)

Bolan, NRHC 2018

Congenital Syphilis Rates (2016)

In 2016, just seven states represented 70% of all congenital syphilis cases in the U.S.

<table>
<thead>
<tr>
<th>State</th>
<th>2012 Cases</th>
<th>2016 Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>35</td>
<td>206</td>
</tr>
<tr>
<td>TX</td>
<td>78</td>
<td>71</td>
</tr>
<tr>
<td>FL</td>
<td>37</td>
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<td>33</td>
<td>48</td>
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<td>GA</td>
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<td>AZ</td>
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<td>15</td>
</tr>
<tr>
<td>IL</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>OH</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td><strong>U.S. Total</strong></td>
<td><strong>334</strong></td>
<td><strong>628</strong></td>
</tr>
</tbody>
</table>

201 of 3,141 counties (6%) reported at least 1 congenital syphilis case in 2016
**Syphilis Screening**

**USPSTF:** Persons at increased risk for syphilis [A]
- MSM (61% of syphilis diagnoses)
- Men and women living with HIV
- History of incarceration
- History of commercial sex work
- Certain racial/ethnic groups (AA > Hispanic > white)
- Being a male younger than 29 years
- Regional variations (hot spots)
What Can Women’s Health Providers Do?

- Check with your local or state health department to determine whether you are in a “hot spot” area
  - Ask your lab to supply a 2-year syphilis positivity rate
- In-service clinicians re: USPSTF syphilis screening guidelines
- Offer screening: intending pregnancy, infertility w/u, IUD or implant removal for pregnancy, preg test visit negative
- Offer treatment for confirmed syphilis cases, or have established referral pathway for treatment
- Collaborate with health department initiatives

HPV Vaccination
Immunization
ACIP: Routine HPV Immunization

Females: HPV Immunization with 9vHPV
Routine: 11- or 12-year-olds

Males: HPV Immunization with 9vHPV
Routine: 11- or 12-year-olds

MMWR Dec 16 2016/ 65(49);1405–1408
ACIP: Routine HPV Immunization

• The series can be given starting at age 9 years
• Catch-up immunization
  – Females 13-26 years old
  – Males 13-21 years old
• Males 22 - 26 years may be immunized

Special Populations:
HPV immunization is recommended thru age 26 for MSM and for immunocompromised persons (incl. HIV infection)

MMWR Dec 16 2016/ 65(49);1405–1408

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ACIP: Routine HPV Immunization

• 2006: administered in a 3-dose schedule
  – Each dose is 0.5 mL, administered IM
  – 2nd dose: 1-2 months
  – 3rd dose: 6 months
• 2016: TWO dose schedule in 9 through 14 year olds
  – Zero and 6-12 months
• Can give with other vaccines (TDaP, TD, MCV4)
• Avoid if a hypersensitivity to yeast or any vaccine component

MMWR Dec 16 2016/ 65(49);1405–1408
Summary of 9vHPV Vaccine

- Original HPV types (6, 11, 16, 18)
  - Non-inferior anti-HPV responses vs 4vHPV vaccine
  - Similar protection against disease
- Additional HPV types (31, 33, 45, 52, 58)
  - 97% protection against disease due to these types
- Adverse effect profile similar to 4vHPV vaccine
- Well tolerated, highly immunogenic in prior HPVv recipients
- Can be co-administered with Menactra and Adacel

Interchangeability of 9v and 4v HPV Vaccine

- *If vaccination providers do not know or do not have available the HPV vaccine product previously administered, or are in settings transitioning to 9vHPV...any HPV vaccine product may be used to continue and complete the series for females*

*MMWR, March 27, 2015; 64(11):300-304*
10/5/18: FDA Approves
Gardasil 9 to 27-45 Year Olds

• 9vHPV studied in 3,200 women 27-45 followed for 3.5 yrs
  – 88% decrease in persistent infection, genital warts, precancerous cervical, vaginal, vulvar lesions (covered types)

• In men 27-45 years, approval was based upon
  – Efficacy data in women for this age group
  – Earlier trials in boys and younger men
  – Immunogenicity data from 150 men in older age group


FDA Approval of Gardasil 9 for 27-45 Year Olds

• Why does it work in older individuals?
  – Even if previously exposed to a few types, can gain protection against HPV types not yet encountered

• CDC ACIP has not modified their guidance yet
  – Will it be recommended or permissive for 27-45 y.o.?
  – Impacts health insurance coverage and no cost-sharing feature of the ACA
HPV Vaccine Coverage (Age 13–17 Years) Is Less Than Other Adolescent Vaccines

NIS-Teen (2007–2014)

"Today, Emily (or Jacob) is due for Tdap, HPV, and MCV4"
Rationale

• We don’t describe or discuss meningococcal vaccine, TDAP or other vaccines like we do HPV
• We don’t have a conversation with the parent about behaviors with any other vaccine
• Behavioral aspects have taken a front seat

The Future

• Cervical cancer (and it’s precursors) will become less common with more widespread HPV vaccination
• The greatest “bang for the buck” is achieved by screening all women for cervical cancer
• Cytology will be replaced with type-specific HPV screening
• Management of abnormal results based on an individual’s viral + risk profile and histopathology
  – Progression risk calculators will replace cytology based algorithms
If high-coverage vaccination and screening is maintained, and if an elimination threshold of four cases per 100,000 women is chosen, cervical cancer is on track to be eliminated as a public health problem in Australia within the next 20 years.
Current Strategies for Screening, Prevention and Treatment of Osteoporosis

Judith Walsh, MD, MPH
Departments of Medicine and Epidemiology and Biostatistics
UCSF

Osteoporosis: Overview

- Definitions
- Risk factors
- Screening and Monitoring
- Treatment
**Background**

- Hip and vertebral fractures are associated with premature mortality
- Any fracture is associated with an increased risk of 5-10 year mortality
- A subsequent fracture is associated with an increased mortality risk for 5 more years
  » Dubbo Osteoporosis Epidemiology Study

**Osteoporosis: Definitions**

- Normal: BMD no lower than 1 SD below mean for young adult women
- Osteopenia (Low bone mass): BMD 1.0-2.5 SD below the mean for young adults
  - (T=-1 to -2.5)
- Osteoporosis: BMD more than 2.5 SD below young adult mean
  - (T<-2.5)
Osteoporosis: Definitions

- T scores vs. Z scores
- T scores compare the patient with the average young adult female
  - Useful for treatment decisions
- Z scores compare the patient with an age matched female
  - Useful for ruling out secondary causes of bone loss

I keep finding these all over the house!

My doctor says bone loss is normal at my age.
Risk Factors

• Age
  – Risk of hip fracture increases with age
  – Older women have a much higher fracture rate than younger women with the same bone density

• Vertebral fractures: very high risk
  – Even if asymptomatic
  – 20% risk of new fracture in the year following a fracture

10-Year Fracture Probability
Age vs. Femoral Neck T-score

Adapted from JA Kanis et al, Osteoporos.Int. 2001;12:989-995
Risk Factors in the WHO Risk Factor Assessment Tool

- Age
- Gender
- Personal history of fracture
- Low body mass index
- Oral glucocorticoids
- Secondary osteoporosis
- Parental history of hip fracture
- Current smoking
- Alcohol intake of 3 or more drinks per day
- Femoral neck BMD

Drugs Associated with an Increased Risk of Osteoporosis

- Thyroid hormone (over replacement)
- Aromatase inhibitors
- SSRIs
- PPIs
- Androgen deprivation agents
- Thiazolidinediones
- Anticonvulsants
Screening and Monitoring

Screening for Osteoporosis

- Bone density is the single best predictor of future fracture
  - Hip BMD is best predictor of hip fracture
- Central dual x-ray absorptiometry (DXA) of spine, hip and body most commonly used and preferred when available
Suzie Jane

• Suzie Jane is a 59 year old woman who has just seen you to establish care. You have gone over her (very long) list of concerns and are getting up to leave the room. She tells you that her mother has osteoporosis and wants to know if she should have a screening test for it.

What is your response?

• No, not until you are 65
• If your mother had a hip fracture, then we should probably order it
• Let’s assess you’re your fracture risk and we can decide
• Hmm….I am not sure (and I am very behind schedule!). Why don’t you come back in a month and we can talk about it then.
Background

• Age is the biggest risk factor for developing osteoporosis

• Screening for osteoporosis is routinely recommended for women aged 65 and older

• Decision making for women <65 with osteoporosis risk factors has been challenging

The News

• Screening for Osteoporosis to Prevent Fractures: US Preventive Services Task Force Recommendation Statement
  –USPSTF JAMA 2018

• AIM: To update the US Preventive Services Task Force Recommendation Statement on Screening for Osteoporosis
Methods

• Evidence review on osteoporosis screening
  – Updating 2011 recommendations
• Review of evidence for screening and treatment
• Review of risk assessment tools

Recommendations

• Screen for osteoporosis with bone measurement testing to prevent osteoporotic fractures in women aged 65 and older
  – Grade B
• Screen for osteoporosis in postmenopausal women <65 at increased risk of osteoporosis as determined by formal clinical risk assessment tool
  – Grade B
• Insufficient evidence for screening in men
  – Grade I
“Formal Clinical Risk Assessment”

- Consider risk factors: parental history of fracture, smoking, excess alcohol consumption, low body weight and menopause status
- For women less than 65 with at least one risk factor, consider using a clinical risk assessment tool
- Consider treatment in women <65 with risk factors who have the equivalent risk of a 65 year old white woman without major risk factors
  - 65 year old white woman, mean height and weight has 10 year FRAX risk of MOF of 8.4%

Risk Assessment Tools

- Simple Calculated Osteoporosis Risk Estimation (SCORE)
- Osteoporosis Risk Assessment Instrument (ORAI)
- Osteoporosis Self-Assessment Tool (OST)
- Osteoporosis Index of Risk (OSIRIS)
Osteoporosis Risk Assessment Tools

- Osteoporosis Self Assessment (OST)
  - Age and Weight
- SCORE
  - Prior Fracture
  - Height, weight
  - Rheumatoid Arthritis
  - Estrogen Use

Summary

- Screen for osteoporosis in women aged 65 and older
  - Grade B
- Screen for osteoporosis in postmenopausal women <65 at increased risk of osteoporosis as determined by formal risk assessment
  - Grade B
  - KEY: Age or presence of particular risk factor does not represent a risk threshold
- Insufficient evidence for screening in men
  - Grade I
NOF : BMD Screening

• Women age 65 and older, men >70 regardless of risk factors
• Adults who have a low trauma fracture after age 50
• In postmenopausal women age 50 to 64
  – Adults with a condition (e.g., RA) or taking a medication associated with low BMD or bone loss
    • ≥ 5 mg prednisone QD or equivalent for ≥ 3 months
  – Historical height loss of 1.5 inches or more (4 cm)
  – Prospective height loss of 0.8 inches or more (2 cm)


Case

• Bonnie Bony is a 68 year old woman who wants to know when she should have her next bone mineral density test. Her last BMD was 2 years ago and showed Osteopenia with a t score of -1.8. What do you tell her?
Choices

1) Let’s schedule it now
2) We should do it in 2 years
3) We should do it in 3 years
4) We should do it in 5 years
5) I have no idea... when do you want to do it?

USPSTF Recommendations

- “Evidence is lacking about optimal intervals for repeated screening”
  - A minimum of 2 years may be needed to reliably measure a change in BMD
  - Longer intervals may be needed to improve fracture risk prediction

»USPSTF
BMD Testing

• Medicare pays for BMD every two years regardless of baseline BMD
• Is repeat BMD useful?
• Does change in BMD provide additional information about fracture risk?

The News

• Bone-density testing interval and transition to osteoporosis in older women.
  – Gourlay et al. NEJM 2012
• Aim: To determine how the BMD testing interval relates to the timing of the transition from normal BMD or osteopenia to the development of osteoporosis before a hip or vertebral fracture occurs
Methods

• 4,597 women from the Study of Osteoporotic Fractures (SOF)
  – Aged 65 and older, population based
  – Study examinations at year 2, 6, 8, 10 and 16
• Outcome: Estimated interval for 10% of individuals to make transition from normal BMD or osteopenia to osteoporosis before a hip or clinical vertebral fracture or treatment for Osteoporosis

Results

• Within each t score range, a percentage of women developed osteoporosis over 15 years

  – Normal 0.8%
    • (-1.00 or higher)
  – Mild Osteopenia 4.6%
    • (-1.01 TO -1.49)
  – Moderate Osteopenia 20.9%
    • (-1.50 to -1.99)
  – Advanced Osteopenia 62.3%
    • (-2.00 to -2.49)
Results/Competing Risk Analyses

• Adjusted interval between baseline testing and the development of osteoporosis in 10% of study participants
  – Normal BMD 16.8 (11.5-24.6) yrs
  – Mild Osteopenia 17.3 (13.9-21.5) yrs
  – Moderate Osteopenia 4.7 (4.2-5.2) yrs
  – Advanced Osteopenia 1.1 (1.0-1.3) yrs

Conclusions

• Osteoporosis would develop in <10% of individuals during rescreening intervals of 15 years for women with normal BMD or mild osteopenia, 5 years for women with moderate osteopenia and 1 year for women with advanced osteopenia

• Future screening recommendations will probably be based on likelihood of osteoporosis progression based on initial BMD
Take Home Message

• Decisions about when to rescreen should be based on the results of initial screening
• Few women with normal BMD will develop osteoporosis at 15 year follow-up
• Back to Bonnie: Would probably wait at least 5 years from her prior BMD

Repeat BMD Screening: The News

• Repeat bone mineral density screening and prediction of hip and major osteoporotic fracture.
• Aim: To determine whether BMD changes after 4 years provide additional information on fracture risk and to quantify the change in fracture risk classification after a second BMD measure
Methods

• Framingham Osteoporosis Study population based cohort of 310 men and 492 women
  – Two BMD measures from 1987 to 1999
• Outcome: risk of hip or major osteoporotic fracture through 2009 or 12 years after second BMD measure
• Net Reclassification Index (NRI):
  – Quantifies change in risk classification after a second BMD measure
  – High risk: Risk of hip fracture 3% or greater or major osteoporotic fracture 20% or greater (vs low risk)

Results

• Mean age 74.8 years
• Mean BMD change -0.6% per year
• Median follow up 9.6 years
• NRI increased proportion classified as high risk by 3.9% and decreased the proportion defined as low risk by 2.2%
• Adding BMD change to a model that included baseline BMD did not improve performance of the ROC curve
  – AUC baseline 0.71 (0.65-0.67) vs 0.72 (0.66-0.79)
Receiver Operating Characteristic Curves for Models Investigating Fracture in Older Adults From the Framingham Osteoporosis Study BMD indicates bone mineral density. All models are adjusted for age, sex, body mass index, weight loss (per pound), and history of fracture measured at the time of the second BMD test. Models are defined in the Methods section.

Figure Legend:
Receiver Operating Characteristic Curves for Models Investigating Fracture in Older Adults From the Framingham Osteoporosis Study BMD indicates bone mineral density. All models are adjusted for age, sex, body mass index, weight loss (per pound), and history of fracture measured at the time of the second BMD test. Models are defined in the Methods section.

Conclusion and Take Home Message

- In untreated men and women with a mean age of 75, a repeat BMD after 4 years did not meaningfully improve the prediction of major hip or Osteoporotic fracture.
- Repeating a BMD after 4 years to improve fracture risk prediction may not be necessary in adults of this age untreated for osteoporosis.
Monitoring Guidelines

• Monitoring for those on osteoporosis treatment
  – What is “treatment failure”?
• ISCD: DEXA spine and hip when expected change in BMD exceeds LSC expected on bone densitometer
  – Every 1-2 years and less often when stable
• NAMS: DEXA hip every 2 years
• Question: What are you going to do?

Monitoring Guidelines

• Prior guidelines recommend follow-up monitoring but no consensus on site or frequency
• ACP Guidelines for women on osteoporosis treatment
  – No bone density monitoring during the 5 year treatment period
OSTEOPOROSIS

Absolute Risk Assessment

WHO Fracture Risk Algorithm

• FRAX
• Calculate the 10 year probability of a hip fracture and the 10 year probability of any osteoporotic fracture
• Includes femoral neck BMD and risk factors
• Can be used only in previously untreated patients
• Can be used with or without BMD
• Algorithm adapted for the U.S.
• Available as an I phone app

www.shef.ac.uk/FRAX
http://www.shef.ac.uk/FRAX/

FRAX™ WHO Fracture Risk Assessment Tool

Welcome

The FRAX™ tool has been developed by WHO to evaluate fracture risk of patients. It is based on individual patient models that include clinical risk factors as well as bone mineral density (BMD) at the femoral neck.

The FRAX™ tool is developed from studying population-based cohorts from Europe, North America, Asia and Australia. In this form, the FRAX™ tool is computer-driven and is available on this site. Several simplified paper versions of the tool are also available and can be downloaded for office use.

The FRAX™ tool predicts the 10-year probability of major fracture. The output is a 10-year probability of hip fracture and the 10-year probability of vertebral fracture (clinical spine, forearm, hip or shoulder fracture).

This is a beta version.

Dr. John A Kanis
Professor Emeritus, University of Sheffield

Links:
International Osteoporosis Foundation: http://www.iofbonehealth.org/
National Osteoporosis Foundation: http://www.nof.org/
Japan Osteoporosis Foundation: http://www.jopf.or.jp/

FRAX™ WHO Fracture Risk Assessment Tool

Calculation Tool

Please answer the questions below to calculate the 10-year probability of fracture with BMD.

Country: US (Caucasian)  Name / ID: [Neil D'Orange]  About the risk factors

Questionnaire:

1. Age (between 55-80 years) or Date of Birth
   Age: 55  Date of Birth: 1953
2. Sex
   Male  Female
3. Weight (kg): 53.5
4. Height (cm): 173
5. Previous fracture
   No  Yes
6. Parent fractured hip
   No  Yes
7. Current smoking
   No  Yes
8. Glucocorticoids
   No  Yes
9. Rheumatoid arthritis
   No  Yes

BMI: 21.2

The 10-year probability of fracture (%)

- Major osteoporotic: 10
- Hip fracture: 1.7

BMI: 21.2
WHO Fracture Risk Algorithm

- Most useful in identifying individuals in the osteopenia range who are most likely to benefit from treatment
- Treat when there is a 10 year risk of hip fracture ≥3% or a 10 year risk of a major Osteoporosis-related fracture that is ≥20% based on the U.S. adapted WHO algorithm
- In the future some BMD machines may be able to provide a report with absolute fracture risk
Question

• Mrs. P is a 66 year old woman who has no previous fracture or other risk factors. Her hip BMD t score is -2.3. She is on no medications. What are your next steps?
  a) Discuss Calcium and Vitamin D intake
  b) Start Raloxifene 60 mg per day
  c) Start Alendronate 70 mg per week
  d) a and c

NOF Treatment Guidelines

Prior hip or vertebral fracture
Other prior bone fracture, or
Secondary medical condition, or
Elevated 10 year fracture risk
No Risk Factors

T-Score

0 -1.0 -1.5 -2.0 -2.5 -3.0
**NOF: Vertebral Imaging**

- Vertebral fractures indicate very high risk
- Consider in women age 70 and over and men aged 80 and over with BMD T score ≤-1.0
- Consider in women aged 65-69 and men aged 70-79 with BMD T score ≤-1.5
- Consider
  - Low trauma fracture during adulthood
  - Long term glucocorticoid use
  - Height loss
    - Historical ≥ 1.5 inch
    - Prospective ≥ 0.8 inch
- No evidence for treatment initiation based on these criteria

**NOF: Osteoporosis Prevention**

- Preventive measures for everyone:
  - Calcium: diet alone or with supplements
    - 1,000 to 1,200 mg a day
  - Vitamin D intake of 800-1,000 IU a day
  - Weight bearing and muscle strengthening exercise to improve agility, strength, posture and balance, increase bone density and avoid falls and fractures
  - Assess fall risk and appropriate modifications
  - Avoid tobacco and excessive alcohol
  - Hip protectors for some at risk?

*2014 NOF Guidelines*
Non-pharmacologic interventions can work!

- Smoking cessation and avoiding alcohol abuse
- Exercise transient impact on BMD but reduces fracture risk
- Hip protectors work
  - Compliance poor even in nursing homes!
- Fall prevention: PT, stop sedating meds
  - RCT home based PT reduced falls by 36%
    - Liu-Ambrose, JAMA 2019

Calcium/Vitamin D

- Women should ideally get RDA for calcium and Vitamin D from diet
- Calcium/Vitamin D are necessary but not sufficient
  - Calcium 1200 mg per day
  - Vitamin D 600-800 IU/d (maximum 4,000 IU/d)
  - Additional therapies (e.g. anti-resorptive therapies) may also be necessary
What do you most commonly use for treatment of Osteoporosis?

- Weekly bisphosphonate
- Monthly bisphosphonate
- Yearly bisphosphonate
- Raloxifene
- PTH
- Denosumab
- Romosozumab

Pharmacologic Therapies

- Estrogen
- Bisphosphonates
- Calcitonin
- SERMs
- Parathyroid hormone
- Denosumab
- Romosozumab
**Estrogen**

- 50% reduction in hip and other non-spine fractures in observational studies
- Estrogen reduced the risk of new vertebral fractures by half in two RCTs
- Reduced hip fracture risk by 34% in WHI
  - No overall benefit even in women at high risk for osteoporosis
- USPSTF does not recommend the use of estrogen for the treatment of any chronic disease
  - Some women may be taking estrogen for other reasons

**Bisphosphonates**

- Four approved in US: Alendronate, Risedronate, Ibandronate, Zolendronate
  - No head to head studies but NMA shows similar efficacy
- New vertebral fracture reduced 50-60%
- Non-spine fracture (including hip) reduced 30-50% if
  - Existing vertebral fracture OR
  - Low hip BMD (T score ≤-2.5)
Bisphosphonates: Adverse Effects

- Osteonecrosis of the jaw
- Femoral shaft fractures

Potential Long-term Side Effect of Bisphosphonates?
Osteonecrosis of the Jaw

• Associated with potent bisphosphonate use:
  – 94% treated with IV bisphosphonates
  – 4% of cases have OP, most have cancer
  – 60% caused by tooth extraction.

• Extremely rare
  – Estimated risk in those treated for osteoporosis
    • 1/10,000 to 1/100,000 person years

• Dental exam recommended before Rx, but no need to stop for dental procedures

Ann Intern Med, 2006
ADA Guidelines, 2011

Osteonecrosis of the Jaw

• 7332 patients receiving oral alendronate in Taiwan
  – 40 cases of ONJ
  – 22 had preceding invasive dental procedures

• Risk increased with longer duration of therapy
  – 0.23% to 0.92% as duration went from 2-10 years

• Risk factors: advanced age, diabetes, rheumatoid arthritis and duration of use

  » Chiu, J Clin Endocrinol Metab 2014
Atypical Femoral Fractures (AFF)

- Long-term BP users (and others)
- Transverse not spiral, cortical thickening, minimal trauma
- Often bilateral, prodromal pain, abn. imaging (x-ray, bone scan/MR)
- ASBMR Task Force (2013)
  Stress fractures. Micro damage?
  Clinical studies: RR for BPs = 2-50
  Risk goes up with longer use and down 1 year after stopping

Re-analysis of Data in 3 RCTs

- 284 hip or femur fractures in 14,195 women
  - 12 were atypical
- Relative hazards
  - RH 1.03 (95% C.I. 0.06, 16.46) for Alendronate in FIT
  - RH 1.50 (95% C.I. 0.25, 9.00) for Zolendronic acid in HORIZON-PFT
  - RH 1.33 (95% C.I. 0.12, 14.67) for continued Alendronate in FLEX
- Conclusions
  - Fracture of subtrochanteric or diaphyseal femur was rare even in women on bisphosphonates for up to 10 years
  - No significant increase in risk but wide confidence intervals

Black et al NEJM 2010
**The News**

- Risk of hip, subtrochanteric and femoral shaft fractures among mid and long term users of alendronate: nationwide cohort and nested case control study
  - Abrahamsen et al BMJ 2016

- Objective: To determine overall safety and efficacy of long term use of alendronate in patients with osteoporosis

**Methods**

- Nationwide population based study in Denmark
- 61,990 men and women aged 50-94 at the start of treatment who had not previously taken alendronate
- Outcomes
  - Fracture of hip, subtrochanteric femur or femoral shaft
- Non-fracture controls matched by sex, year of birth and year of alendronate initiation
Results

- Incidence of subtrochanteric/femoral neck fracture
  - 3.4/1000 person years (95% CI: 3.2-3.6)
- Incidence of hip fracture
  - 16.2/1000 person years (95% CI: 15.8 to 16.6)
- Risk no higher in long term users than in current or past users
- Higher medication adherence and longer duration of use were associated with a reduced risk of hip fracture
  - 0.73 (95% CI: 0.68 to 0.78) for MPR >80%
  - 0.74 (95% CI: 0.56 to 0.97) for use ≥10 years

Conclusion

- The benefit/risk ratio supports a benefit of alendronate even with use for more than 10 years
Take Home

• The overall benefit to risk ratio is favorable for alendronate, even with long term use.

• Long term alendronate use will avert many more hip fractures than will it cause atypical femoral fractures

Case

• Francis Fragile is a 76 year old woman who has been on alendronate for 5 years after having a hip T-score of -2.8. She also has diabetes and hypertension. Her best friend, Veronica Vertebrae, just stopped her bisphosphonate because she had been on it “long enough.” Bonnie wants to know if she should continue taking the alendronate or whether she should stop. What do you tell her?
What do you tell her?

1) Yes, everyone should stop after 5 years of treatment
2) No, you should continue the medication
3) We can stop it if you are having a dental procedure
4) Let’s repeat your bone density and decide
5) I’m not sure. What do you want to do?

FDA View of Long-term Bisphosphonate Use (Sept. 2011)

• Independent review of epidemiologic studies to date and all bisphosphonate trial data…

• FDA conclusions about atypical fractures
  – “conflicting results…causality uncertain”
  – “no agreement on effects of duration or cumulative dose”

• FDA conclusions about ONJ
  – “some evidence that risk increases after 4 yr.”
  – “causality not established”

www.fda.gov, 2011
Bisphosphonates: Duration of Use

• “Bisphosphonates may be safely discontinued in some patients without compromising therapeutic gains but no adequate clinical trials have yet delineated how long the drugs’ benefits are maintained after cessation.”

• “Important Limitation of Use Statement”
  – Optimal duration of use has not been determined
  – Periodic re-evaluation of continued need

The News


• Objective:
  – To provide guidance on bisphosphonate therapy duration with a risk-benefit perspective
Background

• Fracture risk increases with age
• Does continued bisphosphonate therapy continue to confer benefit?  
  – Long half life
• Rare but real side effects
  – Jaw osteonecrosis
  – Atypical femoral fractures
• How long should women remain on therapy?  
  – Drug holidays?
• FDA “Limitation of Use Statement”  
  – Optimal duration of use has not been determined  
  – “All patients on bisphosphonates should have the need for continued therapy reevaluated on a periodic basis”

Methods

• Systematic literature reviews  
  – Two RCTS (FLEX and HORIZON) provide evidence on long term use
• Evaluation of benefits and risks of bisphosphonates and alternatives
Recommendations

• After 5 years of oral bisphosphonates or 3 years of IV bisphosphonates, reassessment of risk should be considered
  – In women at high fracture risk, consider continuation of oral BP for 10 years or IV BP for 6 years
    • High risk based on age (>70 or 75), medication use, new dx of disorder associated with secondary osteoporosis
    • Clinician deemed high risk based on femoral neck T score, age or other risk factors
  – For women not at high fracture risk after 3-5 years of treatment, consider a drug holiday of 2-3 years
• For high risk women, risks of atypical femoral fracture and ONJ are outweighed by reduction in vertebral fracture

What is “high risk?”

• Older women (>70 or 75)
• Low hip T score or high fracture risk score (FRAX criteria)
• Previous osteoporotic major fracture
• Fracture on therapy
• Limitations
  Limited evidence
  White postmenopausal women
  Vertebral fracture reduction only
Impact for practice

• Patients at “low risk” may safely have bisphosphonates discontinued
  – Younger, no fracture history, medication was started for osteopenia, BMD approaching normal?

• Patients at “increased risk” may benefit from continued therapy
  – Older, history of fracture, BMD remaining in osteoporotic range?

• Decisions about when to restart?
  – Role of BMD
  – Currently, no evidence to support use of bone turnover markers

Back to Francis

• Francis is “high risk” based on her age
• Reasonable to continue for 10 years
• Consider BMD?
Monitoring Drug Holidays

• No specific guidance on duration or monitoring

• How to assess?
  – Repeat BMD may be helpful after 3-5 year (FLEX) not sooner
  – Calculate FRAX? No studies

• No data or consensus about re-initiation of anti-resorptive agents or use of newer agents
  – Bauer JEMR 2017; Adler JEMR, 2016

Bea Brittle

• Bea Brittle is a 68 year old woman whom you started on Alendronate two years ago for a hip BMD t score of -2.8. She keeps hearing bad things about the bisphosphonates and wonders if she should switch to a different drug. What do you tell her?
What do you tell her?

1) We should change to PTH
2) We should change to Denosumab
3) We should change to Raloxifene
4) We should change to Zolendronic Acid
5) We should continue the Alendronate

Raloxifene

• Selective Estrogen Receptor Modulators
• Ideally maximize bone and cardiovascular protective effects of estrogen, while minimizing negative effects (endometrial and breast cancers)
**Raloxifene**
- Raloxifene reduces vertebral fractures, but not hip fracture
- Increased risk of thromboembolic events
- Breast cancer prevention
  - Similar to Tamoxifen
- No effect on vaginal bleeding/endometrial cancer

**Calcitonin**
- Intranasal spray
- Increased BMD 10-15% in two years
- Fracture evidence limited and inconclusive
- Analgesic effect in acute osteoporotic fracture
- Oral calcitonin in studies
- Possible increased cancer risk
  - Basal cell and other cancers
Parathyroid Hormone

• Anabolic therapy
  – Vs. anti-resportive
  – Reduces vertebral fractures by 65% and non-vertebral fractures by 53% after 18 months

• FDA approved for postmenopausal women at high risk for fracture

• Safety and efficacy has been shown for 2 years
  – Most BMD gains occur in first few months

• Daily subcutaneous injection

PTH vs. Bisphosphonates

• They have not been compared head to head in a trial that evaluated fracture outcomes

• PTH increased BMD more than alendronate

• PTH is much more expensive

• Long term safety of PTH?
PTH: Adverse Effects

• Hypercalcemia and Hypercalcuria

• Concern for Osteosarcoma
  – Higher doses for longer duration increased risk in rats
  – Case reports of co-existing Osteosarcoma in patients with primary Hyperparathyroidism
  – Only one reported case in post-menopausal woman on PTH

• FDA currently recommends limiting PTH therapy to two years
  – Post-marketing surveillance is ongoing

After PTH...

• PTH is recommended for two years

• Some BMD decline after discontinuing PTH

• Some anti-resorptive therapy should be added after PTH discontinuation
  – Bisphosphonate
  – Raloxifene is an alternative
PTH Alternatives to Daily Injection

- Intermittent PTH
  - 3 months on and 3 months off
- Weekly PTH injection?
- Transdermal patch with 1300 microneedles
  - Phase 2 trial
  - Results in PTH surge and pulsatile effect
  - Increase BMD

PTH: Summary

- Big impact on BMD
- Reduces spine and non-spine fractures compared with placebo
  - Hip fracture?
- Long term safety issues
- Daily injection of an expensive drug
- Consider use in severe osteoporosis when other agents have failed
**Denosumab: FREEDOM Trial**

- Human monoclonal antibody against RANKL
  - RANKL is a cytokine essential to osteoclast function
  - Inhibits osteoclast mediated bone resorption
- 7,868 women with osteoporosis received Denosumab 60 mg or placebo SQ every 6 months for 36 months
- Reduced fracture risk
  - Vertebral fractures (2.3% vs 7.2%)
  - Hip fracture (0.7% vs 1.2%)
  - Non-vertebral fracture (6.5% vs 8.0%)
  - Cummings SR et al.. NEJM 2009: 361: 756-65

**Denosumab**

- FDA approved for the following groups
  - High risk for fracture including androgen deprivation therapy for prostate cancer and aromatase inhibitor therapy for breast cancer
  - Treatment for osteoporosis in postmenopausal women at high risk for fracture
Abaloparatide

- Abaloparatide-Comparator Trial in Vertebral Endpoints (ACTIVE) Phase 3 double blind RCT with 2463 women
- Over 18 months, abaloparatide reduced the risk of new vertebral and nonvertebral fractures
- More information about the benefits and risks needed
  - FDA approved for postmenopausal women with recent osteoporotic fracture (Tymlos®)
- *How does it compare with other osteoporosis treatments?*
  - Miller PD et al JAMA 2016

Romosozumab

- Romosozumab (sclerostin inhibitor) shown in ARCH trial to be associated with a reduction in clinical and vertebral fracture among women with osteoporosis and a fragility fracture
- Treatment was for one year followed by alendronate
- Warning about increased risk of MI, stroke and CV death
- Romosozumab is now FDA approved for use for one year for postmenopausal women at high fracture risk or in whom other treatments have failed
  - Monthly subcutaneous injection
Back to Bea......

- There is currently no compelling reason for her to switch from a bisphosphonate to any other osteoporosis therapy

ACP Guidelines

- Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians
- Issued in May 2017 and updates the 2008 Guidelines
ACP Guidelines

• Offer treatment with alendronate, risedronate, zolendronic acid or denosumab to reduce risk of hip and vertebral fractures in women with known osteoporosis
  – Strong recommendation, High quality evidence

• Treat osteoporotic women with pharmacologic therapy for 5 years
  – Weak recommendation, low-quality evidence
  – “High risk patients may benefit from more than 5 years of treatment”

ACP Guidelines

• Offer pharmacologic treatment with bisphosphonates to reduce risk of vertebral fracture to men with clinically recognized osteoporosis
  – Weak recommendation, low quality evidence

• No bone density monitoring in women during the 5 year treatment period
  – Weak recommendation, low quality evidence
ACP Guidelines

- Recommends against using estrogen, estrogen/progestin or raloxifene for osteoporosis treatment in women
  - Strong recommendation, moderate quality evidence
- Decisions about treating osteopenic women age 65 and older who are at high fracture risk should include patient preferences, fracture risk profile and benefits, harms and costs of medications
  - Weak recommendation, low quality evidence

Summary:
Osteoporosis Prevention

- Avoid or quit smoking and avoid excess alcohol use
- Regular weight bearing and muscle strengthening exercise
- Calcium and vitamin D
- Fall prevention
Summary

• Measure bone mineral density in women aged 65 and older
• Consider risk factors in measuring BMD in younger postmenopausal women
• WHO FRAX tool is useful for absolute risk assessment especially in women with low bone mass
• BMD monitoring frequency should be based on initial BMD and impact on management

Choice of Pharmacologic Therapies

• The Bisphosphonates have been studied most extensively and should remain first line agents
  – Consider stopping after 5 years in “low risk” patients
  – Guidelines about when or whether to stop bisphosphonates remain in evolution

• Raloxifene, Calcitonin PTH and denosumab should remain second line agents
  – Raloifene not recommended by ACP
  – Raloxifene reduces breast cancer risk
Choice of Pharmacologic Therapies

• Calcitonin may be an option for women who decline or cannot tolerate other options or who desire analgesic effect

• PTH or abaloparatide may be an option for women for whom other treatments have failed
  – Treatment for 2 years should be followed by an anti-resorptive therapy

• Denosumab for women with breast cancer on AIs and for high risk postmenopausal women with osteoporosis

• Romosozumab is a new FDA approved option
  – Warning about increased risk of MI, stroke and CV death

Let’s ask the dog…..
Questions?

Thank you!
Common Dermatologic Conditions in Aging Skin

Toby Maurer, MD

The Aging Skin

Normal maturation and sun exposure

- Too much-
  - Tumors, lentigenes, seborrheic keratoses, leg veins, hair, muscle tone
- Too little-
  - Collagen, fat and elastic tissue
Sunscreens- Australian study randomized residents to daily use vs discretionary use between 1992 and 1996
Risk for developing any melanoma reduced by 50% and invasive melanoma risk reduced by 73%
Same trial also showed reduction of risk of developing squamous cell cancer

Tanning Beds
International Agency for Research on Cancer
Comprehensive metaanalysis found that risk of melanoma (skin and eye) increases by 75% when tanning begins before age 30.
Cite this to your young patients
Even though tanners knew the risk, they still used tanning beds-prohibit tanning beds-Finley J Surg Onc 2015
“I’m Here for a Skin Check”

• Can screening by Primary MD reduce morbidity/mortality from skin cancer?
• Hard to do study-need to follow 800,000 persons over long period of time to determine this-studies not done

Bottom line:

• Not enough evidence for or against to advise that patients have routine full body exams BUT
• Know risk factors and incorporate exam into full physical and teach patients what to look for
Actinic Keratosis (AK)

- **Who is at risk?**
  - Over age 35-40
  - Fair-skinned persons
  - Sun-exposed sites
    - Face, forearms, hands, upper trunk
  - History of chronic sun exposure

Clinical Features of AK

- Red, adherent, scaly lesions, usually < 5mm
- Sandpapery, rough texture
- Tender when touched or shaved
- Thick, warty character (cutaneous horn)
Diagnosis of AK

- Diagnosis
  - Clinical features
  - Shave or punch biopsy

Treatment of AK

- Cryotherapy-goal is 2x15 sec thaws
- Topical chemotherapy/chemical peel
  - Efudex (5FU crème) 2x’s/day x 6 wks or
  - Imiquimod-3X’s /wk and 3 mos.

- Photodynamic therapy
Diagnosis of BCC: Shave or Punch Biopsy

Recommended Treatment of BCC

- Surgical excision (head and neck)
- Curettage and desiccation (trunk)
- Radiation therapy (debilitated patient)
- Microscopically controlled surgery (Mohs)
  - Recurrent/sclerotic BCC’s
  - BCC’s on eyelid and nasal tip
    - Recurrent widespread BCC-oral Vismodegib
Aldara (Imiquimod)

- Topical therapy designed for wart treatment
- Upregulates interferon/ down regulates tumor necrosis factor/works on toll like receptors
- Seems to have efficacy in superficial BCC’s
- Do Not use in BCC’s that are nodular or invasive
- Biopsy to confirm diagnosis *BEFORE* treatment

Squamous Cell Carcinoma (SCC)

- Who is at risk?
  - Age 50+
  - Chronic sun exposure
    - Head, neck, lower lip, ears, dorsal hands, trunk
  - Special circumstances
    - Immunosuppression (organ transplant)
    - Radiation therapy
Clinical Features of SCC

• Papule, nodule or tumor
• Non-healing erosion or ulcer
• Cutaneous horn (wart-like lesion)
• Fixed, red, scaling patch/plaque (Bowen’s-SCC-in-situ)

How to Diagnose

• Punch or excisional/incisional biopsy
• Shave biopsy for flat, non-elevated lesion
Treatment of SCC

- Recommended treatment
  - Excision
  - Radiation therapy (in debilitated patient)
  - Follow-up for SCC-1-3 months for 2 yrs then q 4-6 months for 5 yrs

METASTATIC Disease:
Cetuximab/EGFR blockers
PD-1 inhibitors

Melasma

- Hyperpigmentation of cheeks, chin, forehead
- Seen in pregnancy and in hormone replacement
- Also seen in females and males without hormone treatment
- Treatment - Hydroquinone 4% and SUNSCREEN-4 months on / 4 months off to prevent ochronosis
Dry skin on feet

- Keratoderma climacterum—seen in menopause/post-menopause
- Often present with deep fissures
- Urea 40% /topical steroid

Lichen simplex chronica

- Often seen on the labia
- Pts have had multiple anticandidal treatment
- Stop itch /scratch cycle with potent topical steroids
- Stop the washing/cleaning habits
Pruritus and Xerosis

- Aging skin loses it’s barrier functions and gets drier and itchier
- New onset dryness and itchiness in the elderly - CBC, TSH, LFT’s and renal function
- Lubrication is key
- Decrease water use, NO soap
  - Sedating antihistamines such as benadryl, atarax, doxepin are useful

Treatment

- ACV 800 mg 5 x’s/day
- Famvir 500mg tid
- Valacyclovir 1000 tid
- begin within 48 hrs of onset of blister. Any time in immunosuppressed host
- Pain control
  - NSAIDS/Tylenol
  - Neurontin: 100 mg tid
  - Elavil: 25 mg qhs or q 8 hrs
- Prednisone: no role
Herpes Zoster

- Zoster vaccine available – boosts older person’s cell-mediated immunity to VZV
- Study done on 38,000 persons 60 yrs and older (Kimberlin et al NEJM March 2007)
- Incidence of zoster was 51% lower in those that received vaccine vs placebo
- Post-herpetic neuralgia was 67% lower in vaccinated group
- Worked best in 60-69 yr olds

- Can it be used in pts with previous zoster-yes
- How about use in younger age groups? 50 and above now being looked at
- Needs to be give within ½ hour of reconstitution
- $190.00 for injection (ave)
-uptake in most communities is only around 30%
-recommended now before giving patients immunosuppressive drugs like MTX or TNF blockers.

Blistering Diseases
• Most common in the elderly is BULLOUS PEMPHIGOID
• Can be localized or widespread blistering
• Biopsy
• Start prednisone 60-80 mg daily and taper over months
• Add steroid sparing drugs like mycophenolate or azathioprine
• Always keep pt on at least low dose prednisone
Too Much Hair

• Vaniqa
  – topical cream that breaks the chemical bond of hair
  – apply 2x’s/day forever
  – 30% effective
  – $30/month

Hair Removal

– pigment of hair absorbs the light and gets destroyed
– dark hair responds
– hair is always in different growth phases, so treatment has to be repeated several times to catch the phase (expensive)
– pigment changes of surrounding skin and scarring
– fast and minimal scarring
Hair Loss

• If not scarring and diffuse:
• Check recent surgeries/illness, nutrition, anemia, TSH, estrogen replacement, medication history, VDRL.
• If hirsute with scalp hair loss - DHEAS and free testosterone
• If lactating - check prolactin

If all negative

• Androgenetic Alopecia - Minoxidil 5% bid topically (even in women)
  Can make hair oily - may want to start with minoxidil 2% or use 2% by day and 5% at night
  Minoxidil foam – once at night
  Use for at least 6 months for results and what you see after 1 yr. is the effect you can expect.

  What about finasteride (propecia)? - Does not work in women - in men the dose is 1 mg qd.
Androgenetic Alopecia

Men

Women

Protein Rich Plasma
- Spin down pt’s own blood
- Reinject plasma into scalp for alopecia
- Smear the remaining buffy coat on the face
- Growth factors?
- Evidence-22 papers-no proven benefit
Stop the Motion

• Botulinum Toxin
  – FDA approved (two types available)
  – paralyzes muscles so that the wrinkles relax
  – excellent for crow’s feet, glabellar wrinkles, and nasolabial fold
  – ptosis and necrosis if not done right
  – lasts for 3 months

Build up the understructure

• Can you build collagen with creme?
• Retinoids (topical): with daily use over long periods of time, may increase the thickness of collagen
• Retin A- 0.025-0.1 %. Start with crème and move to gel
To Fill and Create Understructure

- Collagen
- Hyaluronic Acid (Restalyne)
- Silicone
- Poly-L-lactic Acid (Sculptra)
- Polymethacralate (Artefill)
- Fat Transfer-pts own material

Points to consider

- Allergy testing
- Pain on injection-some of these have preservatives
- Overcorrection vs undercorrection-pts are happier after they leave office overcorrected with non-permanents
Cautionary points

• Technique important-send to practitioners in the know-nonpermanent fillers are more forgiving; permanent fillers, technique is everything
• Expensive
• May need touch-ups
• Can form granulomas

Ablative Therapy

• Involves wounding the skin with chemicals or light (laser)
• Take into account skin type and amount of damage from sun and aging
What can primary provider do to help?

- If pt has h/o orolabial HSV-prophylax with ACV
- If pt has been on accutane-no procedure for at least 6 months after stopping
- If pt has psoriasis-reconsider so as not to have psoriasis spread to face after a procedure
- No bacterial antibiotic prophylaxis is needed
- Sunscreen before and after procedure

Economics

- Most providers using these techniques will use a combination-i.e.-they will fill in some cracks, ablate tumors and stop the motion
- Costly and NOT covered by insurance
- Beware of gimmicks
- Expectations are often high-many providers who are good will spend time understanding expectations and discuss reality and cost
- Lawsuits are very common
- Addiction to procedures not uncommon
Body Dysmorphic Syndrome

- Patients complain of ugliness/physical flaws
- Thinking about this consumes many hours of their day
- Very dissatisfied with providers-onus is on doctor to figure it out
- Recognition by providers is helpful although patients often deny situation
- Conveying to patient that treatment (other than cosmetic) will help with functionality

- SSRI’s have been helpful in some studies-usually high dose for at least 12 weeks
- Cognitive behavioral therapy has also been helpful in small studies-time consuming and expensive-pts keep journals of their behavior, substitute pleasurable behaviors, keep track of lapses and what made them lapse
Depression in Primary Care:

Mourning and Melancholia

Descartes Li, M.D.
Clinical Professor
University of California, San Francisco
descartes.li@ucsf.edu

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none
Outline

- Introduction and Epidemiology
- “Normal sadness”
- Trap of Meaning
- Antidepressant controversy and Placebos
- Stepped pharmacotherapy of depression (STAR*D)
- Exercise, Light Therapy, Bibliotherapy
Prevalence in U.S.:

1 year = 6.6%
   (13.1-14.2 million)

Lifetime = 16.2%
   (32.6 – 35.1 million)

Face-to-face household survey, n = 9090

Kessler, RC et al. The Epidemiology of Major Depressive Disorder: Results From the National Comorbidity Survey Replication (NCS-R). JAMA. 2003;289:3095-3105.

Prevalence of Psychiatric Disorders*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime prevalence(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any mood disorder</td>
<td>19.54</td>
</tr>
<tr>
<td>Major depression</td>
<td>16.54</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>4.30</td>
</tr>
<tr>
<td>Bipolar I</td>
<td>3.31</td>
</tr>
<tr>
<td>Bipolar II</td>
<td>2.33</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>16.16</td>
</tr>
<tr>
<td>Social anxiety</td>
<td>4.97</td>
</tr>
<tr>
<td>Any drug use disorder</td>
<td>10.33</td>
</tr>
</tbody>
</table>


The prevalence of MDD:

4.4%

in both 1990 (4.2–4.7%) and 2010 (4.1–4.7%).
Outline

- Introduction and Epidemiology
- "Normal sadness"
- Trap of Meaning
- Antidepressant controversy and Placebos
- Stepped pharmacotherapy of depression (STAR*D)
- Exercise

Case Vignette A

72yo man is depressed in the context of the death of his wife.

How long would you wait before diagnosing MDD?
Assume he meets DSM-5 criteria for MDE.

a) Two weeks
b) One month
c) Two months
d) Six months
e) One year or more
Mourning and Melancholia

Outwardly can look the same

Melancholia:
- No conscious object loss
- Loss of self-regard, but not ashamed
- Difficulty with nourishment, digesting
- Difficulty with sleeping

“Normal Sadness”

Per Horvitz and Wakefield, 3 criteria:
1. Has an environmental trigger
2. Roughly proportionate in intensity to loss
3. Ends when loss situation ends

Problems with “normal sadness”

1. What constitutes a trigger?

2. When is the response *proportionate* to the loss?

3. Does the presence of a recent major loss somehow make it more likely that depression will spontaneously resolve?

Resilience to Spousal Loss

“…resilience in the face of spousal bereavement is less common than previously thought”

-Only 8% showed resilience across all five indicators of life satisfaction and general health functioning

Depression vs. Grief

Individuals who fulfill MDD criteria after loss of significant other have NOT been shown to recover at a greater rate than MDD alone

What the DSM-5 says about bereavement

Grief is still exists, but depressive episodes must be diagnosed independently of loss

Grief and MDD are different and therefore they should be distinguished separately

Depression vs. Grief

<table>
<thead>
<tr>
<th></th>
<th>MDE</th>
<th>Grief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant affect</td>
<td>Depressed mood</td>
<td>Emptiness and loss</td>
</tr>
<tr>
<td>Affect</td>
<td>Persistently depressed</td>
<td>Waves or &quot;pangs of grief&quot;</td>
</tr>
<tr>
<td>Accompanied by</td>
<td>Pervasive unhappiness or misery</td>
<td>Humor, positive emotions</td>
</tr>
<tr>
<td>Thought content</td>
<td>Self-critical or pessimistic ruminations</td>
<td>Preoccupied with thoughts/memories of deceased</td>
</tr>
<tr>
<td>Feelings of worthlessness</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Yes</td>
<td>(except may hear voice of deceased)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Yes</td>
<td>(except about &quot;joining&quot; the deceased)</td>
</tr>
</tbody>
</table>

Case Vignette A

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• Exercise

Case vignette B

28yo man, recently married 6m ago, appears well, but quickly breaks down: He says he’s made a terrible mistake for imposing himself on his wife. *I’m a terrible person who cheated on my wife and on my taxes.* He reports two months of depressed mood, crying spells, as well as oversleeping and not being able to get out of bed. In addition, his energy has been low, he has no appetite, and he can’t focus at work.

Would you diagnose him with Major Depressive Disorder? Would you prescribe an antidepressant?
Case vignette

“I cheated on my wife and on my taxes.”

Do we accept his reasons as the causes of his depression?

Even when confronted with an intuitively plausible set of reasons, we must look for objective causes.

Reason vs. Cause

What the difference?

Reason : (noun)
( 1 ) Motive or justification for something
“Give me the reason for your going.”
“He has adequate reason for doing so.”

Cause : (noun)
( 1 ) That which produces an effect, thing, event, person, etc...make something happen
What was the cause of the fire?
Smoking is one of the causes of heart disease.
The Trap of Meaning

“Finding an explanation that appears meaningful and adopting it as causal.”


"...humans are incredibly good at linking cause and effect—sometimes too good..."

"...it means that when you see something occur in a complex adaptive system, your mind is going to create a narrative to explain what happened—even though cause and effect are not comprehensible in that kind of system."

Life Events have **NOT** been associated with MDD

"in general, MD can be diagnosed independently of the psychosocial context in which it arises."


What are the Validated Risk Factors for Depression?

- Neuroticism
- h/o GAD
- h/o phobia
- h/o panic disorder
- age of onset of MDD
- parental warmth

- childhood sexual abuse
- parental loss
- maternal h/o MD
- paternal h/o MD
- h/o MD in cotwin
- prior episode of MD
Take Home Message

Be aware of "explaining away" mood episodes.

Anticipate patient’s explanatory model and adherence implications


Outline

• Introduction and Epidemiology
• “Normal sadness”
• Trap of Meaning
• Antidepressant controversy and Placebos
• Stepped pharmacotherapy of depression (STAR*D)
• Exercise
THE EMPEROR’S NEW DRUGS
Exploding the Antidepressant Myth
IRVING KIRSCH, Ph.D.

Prevalence of antidepressant usage

Figure 2. Percentage of persons aged 12 and over who take antidepressant medication, by race and ethnicity and by family income group: United States, 2005–2008

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>13.6</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>3.9</td>
</tr>
<tr>
<td>Mexican American</td>
<td>2.7</td>
</tr>
<tr>
<td>Less than 100% of poverty level</td>
<td>10.5</td>
</tr>
<tr>
<td>100% to less than 200% of poverty level</td>
<td>10.8</td>
</tr>
<tr>
<td>200% or more of poverty level</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*Significantly different from non-Hispanic white population.

NOTE: Access data table for Figure 2 at: http://www.cdc.gov/nchs/data/databriefs/db176_tables.pdf#2

Is there a glut of coffee, alcohol?
How about insulin, Lipitor?

**Increased antidepressant usage associated with a decrease in overall suicide rates**

Olsson M, Shaffer D, Marcus SC et al. (2003), Relationship between antidepressant medication treatment and suicide in adolescents. Arch Gen Psychiatry 60(10):978-982.

**In Defense of Antidepressants**

American Psychiatric Association  
Practice Guidelines for Depression  
Agency for Health Care Policy and Research,  
Clinical Practice Guidelines  
Cochrane Review  
http://www2.cochrane.org/reviews/en/ab007954.html  
"In Defense of Antidepressants”, by Peter Kramer (The New York Times, July 9, 2011)  

**Bottom Line:** Antidepressants often do help, but for mild depression, watchful waiting is a reasonable option

---

**Placebos**

Adherence to placebo is associated with decreased mortality

A confounder?

Simpson SH et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006; 333  
doi: https://doi-org.ucsf.idm.oclc.org/10.1136/bmj.38878.67848.55 (Published 29 June 2006)
Response to Placebo and Clinical Management Declines with Initial Severity
Mean Standardized Improvement as a Function of Initial Severity


Antidepressant and Placebo Response Rates
(N=36,385; 251 drug-placebo pair-wise comparisons)

Another example: the largest placebo-controlled antidepressant trial in late life depression

728 Patients with Late Life Depression


Placebos are NOT nothing

The Largest Drug vs Placebo Study in 728 Patients with Late Life Depression

How do placebos work?

Opioid receptors

Expectancy and conditioning

Regression to the Mean

Placebos

Time average participant in an 8-week trial spends with top experts and highly trained caregivers:

20 hours
Placebos: Bottom Line

Placebos are potent.

The “placebo” in any study should be examined carefully.

Bottom Line: The milder the depression, the more difficult it is for treatments to separate from placebo.
Outline

• Introduction and Epidemiology
• “Normal sadness”
• Trap of Meaning
• Antidepressant controversy and Placebos
• **Stepped pharmacotherapy of depression (STAR*D)**
• Exercise

Disclosures

still none
STAR*D
Sequenced treatment alternatives to relieve depression

2,876 outpatients started on citalopram
- exclusions: schizophrenia, bipolar disorder, eating disorders, OCD
- Not placebo-controlled, therefore unblinded

Level 1

- Obtain Consent
  - CIT
  - Follow-up

Level 2

Randomize

Switch Options
- SER
- BUP-SR
- VEN-XR
- CT

Augmentation Options
- CIT + BUP-SR
- CIT + BUS
- CIT + CT
<table>
<thead>
<tr>
<th>Level</th>
<th>Medication</th>
<th>Average Dose</th>
<th>Remit Rate QIDS-SR ≤ 5</th>
<th>Response Rate 50% Reduction of Baseline QIDS SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Citalopram</td>
<td>41.8mg/d</td>
<td>33%</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Switch</td>
<td>Bupropion-SR</td>
<td>28.3mg/d</td>
<td>25.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sertraline</td>
<td>136mg/d</td>
<td>26.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine XR</td>
<td>194mg/d</td>
<td>25.0%</td>
</tr>
<tr>
<td></td>
<td>Augment</td>
<td>Bupropion SR</td>
<td>268mg/d</td>
<td>39.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Buspirone</td>
<td>40.9mg/d</td>
<td>32.9%</td>
</tr>
<tr>
<td>3</td>
<td>Switch</td>
<td>Mirtazapine</td>
<td>42.1mg/d</td>
<td>12.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nortriptyline</td>
<td>96.8mg/d</td>
<td>19.8%</td>
</tr>
<tr>
<td></td>
<td>Augment</td>
<td>Lithium carbonate</td>
<td>900mg/d</td>
<td>13.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3 50mcg/d</td>
<td>24.7%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Tranylcypromine</td>
<td>36.9mg/d</td>
<td>13.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Venlafaxine+mirtazapine</td>
<td>210.3mg/d+35.7mg/d</td>
<td>15.7%</td>
</tr>
</tbody>
</table>

**Take homes from STAR*D**

- Switching to Bupropion-SR, Sertraline, or Venlafaxine XR equally efficacious (remit rate for all: about 25%);
- No difference between different classes of antidepressants
- Augmentation with Bupropion (39% remission rate) slightly better than buspirone (33%)
- Third and fourth level remission rates less than 20%, except T3 augmentation.
Remember Tricyclics

- amitriptyline (Elavil)
- imipramine (Tofranil)
- nortriptyline (Pamelor)
- desipramine (Norpramin)

Thyroid augmentation

**T-3, (Cytomel)**

Dosing schedule:
- 12.5mcg/day x2days
- 25mcg/day x2days
- 37.5mcg/day x2days
- 50mcg/day x2days

In STAR*D, T3 was started at 25 μg/day for 1 week and then increased to the recommended dose of 50 μg/day.
Results: Remission rates were 15.9% with lithium augmentation and 24.7% with T3 augmentation.*not statistically significant

Bonus tip#1: Light Therapy

Check out the Center for Environmental Therapeutics: www.cet.org

More on this in Sleep talk

Bonus tip#2
Bibliotherapy:
• Feeling Good, by David Burns
• Mind Over Mood, by Greenberger and Padesky
Outline

- Introduction and Epidemiology
- “Normal sadness”
- Trap of Meaning
- Antidepressant controversy and Placebos
- Stepped pharmacotherapy of depression (STAR*D)
- **Exercise**

“Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it.”

~Plato
Exercise:
Lack of exercise associated with anxiety and depression


How much exercise is enough?

Exercise Dosage: High vs. Low

<table>
<thead>
<tr>
<th>3x/week “control”</th>
<th>flexibility exercises</th>
</tr>
</thead>
<tbody>
<tr>
<td>“low-dose” (LD)</td>
<td>7 kcal/kg/week (490 kcal*)</td>
</tr>
<tr>
<td>“public health dose” (PHD)</td>
<td>17.5 kcal/kg/wk (1225*)</td>
</tr>
</tbody>
</table>

Total patients = 80
*for 154 lb person

Calories per hour by activity

<table>
<thead>
<tr>
<th>Activity (1-hr)</th>
<th>Weight of person</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>160 lbs</td>
</tr>
<tr>
<td>Bicycling, &lt; 10 mph, leisure</td>
<td>292</td>
</tr>
<tr>
<td>Basketball game</td>
<td>584</td>
</tr>
<tr>
<td>Running, 5 mph</td>
<td>606</td>
</tr>
<tr>
<td>Running, 8 mph</td>
<td>861</td>
</tr>
<tr>
<td>Swimming, laps</td>
<td>423</td>
</tr>
<tr>
<td>Walking, 2 mph</td>
<td>204</td>
</tr>
<tr>
<td>Walking, 3.5 mph</td>
<td>314</td>
</tr>
</tbody>
</table>
Findings: LD vs PHD


Exercise 2012: A Systematic Review

Overall long-term (> 6m) adherence to exercise program is poor at 50%

Some studies had adherence rates better than 50% but likely product of selection bias (i.e. patients volunteered for study, motivated to exercise)

Exercise 2012: A Systematic Review

Conclusions:
Exercise improves depressive symptoms
Unclear by how much
Probably have to maintain


For info on starting exercise, including frequency and intensity, see uptodate.com’s public access patient website:
https://www.uptodate.com/contents/exercise-beyond-the-basics
Exercise: Bottom Line

- Easy to say, not easy to do
- Subject selection in studies may be key.

Summary

- Introduction and Epidemiology
- “Normal sadness”
- Trap of Meaning
- Antidepressant controversy and Placebos
- Stepped pharmacotherapy of depression (STAR*D)
- Exercise
“My treatment fails only in incurable cases.”

-Galen
129 AD – c. 216

More slides on exercise
Findings: LD vs PHD

Where did the study individuals come from?

Had to “pre-screen” 1664 people to get 80
Exercise in care homes 2013

**Intervention:**
- depression awareness training for care-home staff, 45 min group exercise sessions (delivered twice weekly)
- whole home component designed to encourage more physical activity in daily life.

**Control:**
- depression awareness training only

Findings

no evidence of a difference for
• GDS-15 scores*
• MMSE
• fear of falling
• EQ-5D (tables 5, 6)
• Antidepressant use
• mental health
• care team visits

*irrespective of whether residents were depressed at baseline.
Conclusion

“This evidence does not support the use of this type of intervention to reduce the burden of depressive symptoms in residents of care homes, and alternative strategies for this common and important problem are needed.”


2015 Exercise for depressed elders

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age 65–85 years</td>
<td>• other Axis I diagnoses,</td>
</tr>
<tr>
<td>• Major depressive disorder with (HRSD) &gt;18</td>
<td>• substance or alcohol misuse,</td>
</tr>
<tr>
<td>• Being sedentary*</td>
<td>• cognitive impairment,</td>
</tr>
<tr>
<td></td>
<td>• physical illness that prevents exercise</td>
</tr>
</tbody>
</table>

*less than 30 min on five days each week or less than 20 min on three days each week vigorous intensity aerobic activity (2007 AHA)

# Protocol for the non-progressive exercise intervention

<table>
<thead>
<tr>
<th>Each session</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min warm-up: walking, strengthening exercises, quiet calisthenics</td>
</tr>
<tr>
<td>2 reps X10 min each: mat work: stretching, calisthenics, breathing exercises</td>
</tr>
<tr>
<td>2 reps X5 min each: instrumental exercises (first w/ ball, then w/ stick)</td>
</tr>
<tr>
<td>2 reps X5 min each: balance exercises (e.g. toe walking, heel to toe, single limb stance, staggered stance)</td>
</tr>
<tr>
<td>10 min cool down: walking, quiet calisthenics</td>
</tr>
<tr>
<td>rest when &gt;70% of peak heart rate, or whenever they felt exhausted</td>
</tr>
</tbody>
</table>

# Protocol for the progressive aerobic exercise intervention

<table>
<thead>
<tr>
<th>Each session</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min warm-up: breathing exercises, slow cycling.</td>
</tr>
<tr>
<td>Exercise to percentage of the peak heart rate (PHR) per Vmax test Then 5–10 min of cool-down cycling.</td>
</tr>
<tr>
<td><strong>weeks 0–4:</strong> cycling at 60–70% PHR, 30–40 min</td>
</tr>
<tr>
<td><strong>weeks 5–8:</strong> treadmill exercise at 70–80% of PHR, 40–50 min</td>
</tr>
<tr>
<td><strong>weeks 9–12:</strong> 5 sessions of 5 min at 85% of PHR or 40 min of continuous treadmill at 70% of PHR</td>
</tr>
<tr>
<td><strong>weeks 13–24:</strong> five interval training sessions of 6 min at 85% of PHR, or 40 min of continuous treadmill at 70% of PHR</td>
</tr>
</tbody>
</table>

---

Remission rates

<table>
<thead>
<tr>
<th></th>
<th>@12 weeks</th>
<th>@24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline only, n = 42</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>Ser+nonprogressive exercise, n = 37</td>
<td>54%</td>
<td>73%</td>
</tr>
<tr>
<td>Ser+progressive aerobic exercise, n = 42</td>
<td>83%</td>
<td>81%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

2015 exercise for depressed elders

Sertraline only = 50mg/day
Exercise Groups = three sessions per week (60 min duration) for 24 weeks

Nonprogressive exercise (NPE)
Progressive aerobic exercise (PAE)
2015 exercise for depressed elders

Discussion

- beneficial effect independent of the severity and chronicity of depression
- Exercise best along with an antidepressant
- After adjusting for confounders, the outcomes of depression were similar in the two exercise arms
- did NOT observe significant improvement in aerobic capacity in the exercise groups

Dermatologic Procedures

Toby Maurer, MD

• Liquid nitrogen
• Intraleisional steroids
• Unna Boots
• Biopsies-snip, shave, punch
• .....scabies prep and KOH preps
The Gun vs. The Q-Tip

• Cost:
• Gun delivers more constant pressure
• Gun is faster if you have the volume

Liquid Nitrogen

• Thaw time is key
• Thawing destroys the cells
• Freeze to get sustained ice ball & adequate thaw time
• Thaw time - From time the lesion is white until it goes back to normal color
• Always do 2 cycles of thawing
Liquid Nitrogen (cont’d)

- Thaw times differ by location
  - Face/genital 2 x 15 sec. thaws and dorsal arms
  - Palms/soles 2 x 30-45 sec. thaws
- Thaw times differ by diagnosis
  - Seborrheic keratoses - 15 sec. thaws
  - Actinic keratoses - 15 sec. thaws
  - Warts - need more & want to go 1mm around periphery

Know what you are freezing

- Check that pt has resoltuion of lesion-
  document that you told them or that you are bring them back
Side Effects

- So cold it feels like a burn
- Blister tonight then crust that will take 5 days to resolve (15 sec. thaws) vs. 10 days (30-45 sec. thaws)
- Can break the blister
- Warn re: hypo/hyperpigmentation in persons w/underlying pigment

Intralesional Steroids

- Used for keloids, hypertrophic scars, patches of alopecia areata
- Trick is not to go into fat but stay in dermis (don’t want atrophy)
- Warn patient and document potential side effects like pigment change and atrophy
- For alopecia areata -10 mg/cc; 1-3 cc per month
- For Keloids-20-40 mg/cc; 1 cc per month
Keloids

- Intraliesional steroids-20-40 mg/cc
- Pts will absorb steroids systemically so limit is 40 mg per month
- Anaesthetize surface with lidocaine and epinephrine using 30 gauge needle
- Get into the right space and inject steroid with 22 gauge needle

How to do a KOH

- Scrape the area and GET LOTS of scale-use a 15 scalpel
- Place cover slip on top of scale
- Put a drop of KOH on the side of the cover slip and let it go under the slip by osmosis
- Heat the specimen not to point of boiling (Important to do when you have dry skin)
- Use your pen to put pressure on cover slip to separate the cells
- Bring your condensor all the way down
- Use 4x power and MAX of 10 x power to look for hyphae
Scabies Prep

- Why do it? Not everything that itches is scabies *Tip:* itchy nodules on penis = scabies
- Don’t rely on finding a burrow but if you do, scrape it-high yield
- Highest yield areas-between the fingers, wrists, scapula, lateral edge of the feet-look for papulovesicular lesions that are primary (not scratched)
Juice and scale go on slide, place cover slip on top
Mineral oil is great but water will do
Bring condenser all the way up
Look at every part of slide and especially around cover slip edges
Unna Boots

• For venous ulcers when there is edema
• Make sure there is no cellulitis before you cover an area
• You will need:
  Currette, +/- lidocaine (no epi), metrogel, duoderm, allevyn, unna boot
Unna Boots

- Never too tight
- Leave folds in place
- Anchor joints
- Start at mid foot and work up to the knee
- Coban layer on outside
- If pt notes pain, take dressing off
BIOPSIES

- Pathologists are only as good as the clinician
- REFER - If you have no idea what you are looking at, neither will the pathologist.
- Must include history, location and DIFFERENTIAL diagnosis—what are you ruling out AT LEAST

Biopsy Tips

- Give your pathologist an adequate and representative sample
- Choose a lesion that has not yet evolved
- Don’t crush the tissue
- If your results don’t make sense, call the pathologist or a dermatologist for review
- Billing: procedural code for biopsy (including closure)—neoplasm of uncertain behavior
• NUMBING IS STANDARD OF CARE
• 1% Lidocaine and epinephrine
• Epi-okay to use on fingers, toes, and penis unless using large doses
• Do not use Epi in Reynauds or other vascular problems (lower leg vascular insufficiency)
• EMLA in Kids followed by IL numbing
• Lidocaine allergy
• IL Benadryl

Informed Consent

• Why are you doing this?
• What could be done instead?
• Risks involved
  – Scar
  – Infection
  – Bleeding
Snip Biopsies/Excision

- Scissor snip
- Skin tags
- AlCl for hemostasis
- Send to pathology
- Do NOT use silver nitrate or Monsels on visible skin

Shave Biopsies

- Leave half of lesion behind so you know to where to return for definitive treatment
- Puff up section with anesthetic and LIGHTLY pick up with forceps-scalpel cuts under skin
- Al Cl for hemostasis
- Petroleum jelly/bandaid
Shave biopsy
Punch Biopsies

• Allows you to get to the top of the fat
• You will get the epidermis and dermis
• Use for diseases that go into the dermis from the epidermis or that originate in the dermis. (Hint: There is a palpable or papular/ nodular component.)

Punch Biopsy

• Punch (sizes 2-6mm)
  – 2mm - Not enough info for pathologist
  – 3 mm - Use in cosmetically sensitive areas
  – 4mm - Standard
  – 5-6mm - Use to get around lesion or if submitting part of a biopsy for tissue culture
Punch Biopsy - You Will Need

- Non-absorbable suture
  - 2mm & 3mm - one stitch
  - 4mm - two stitches
  - 5mm and 6mm - three stitches
  - GELFOAM

How to make a hole oval?

- All in skin tension lines
Suturing

- Interrupted adequate
- Double knot for first throw then 3 more single knot throws
- Remove sutures in 3 days face, 7 days back, chest and 10-14 days limbs
- Petroleum jelly/bandaid-keep wound dry

Excisional Biopsies

- You have control
- Go down to fat, through fat to fascia & beyond
- Lets you get around the lesion entirely
  - Malignant melanoma
  - r/o Dysplastic nevus vs. malignant melanoma
  - Vasculitis
  - Panniculitis
  - Epidermoid cysts
• Mark it with pen before putting in anesthetic
• 3:1 rule-measure lesion- If 1 cm, then will need total length to be 3 cm (1.5 cm on each side) for proper closure
• Don’t bevel blade—should be perpendicular

• Undermine edges for larger wounds—helps to close
Women’s Health: 
Year in Review

Judith Walsh MD, MPH 
Professor of Medicine and 
Epidemiology and Biostatistics 
May/June, 2019

Update in Women’s Health

• Annual review presented at Society for General Internal Medicine Annual Meeting 
  – May, 2019 Washington DC
• Brigid Dolan, MD, Northwestern University
• Sarah Merriam MD, University of Pittsburgh
• Bimla Schwarz MD, UC Davis
Plan for today...

• Review some of the most significant published advances in the Women’s Health medical literature over the past year (and a bit!)
  – Top articles
  – Key articles
  – Guidelines

• Assess the strength and scope of the evidence presented in the selected literature

• Apply this new information to our clinical practice
  – Take-home points

Process

16 Journals March 1, 2018 – March 31, 2019
4 Independent reviewers: ranked 1-4 stars
Criteria

- How new/innovative is this information?
- Strength of the evidence?
- How will it change my practice?
- What is not covered elsewhere?

Topics

- Bone and Joint Health
- UTIs and Incontinence
- Thromboembolic Disease
- Pregnancy Associated Health
- Thyroid Disease
- Cervical Cancer Screening
- Contraception
Bone and Joint Health

Osteoporosis: Treatment
Betty Brittle

- Bea is a 66 year old woman who had a DEXA last year with a t score at the hip of -2.3. She has just learned that her mother, who is 91, has fallen and sustained a hip fracture. She is worried about her bones and wonders if she should start a medication for osteoporosis.

What do you say to Bea?

- Keep taking Vitamin D and calcium
- Let’s start alendronate right now!
- We don’t start treatment until you have osteoporosis (t score <-2.5)
- Hmm. I think there was a paper about this but I am not sure....what do you want to do?
Background

• Evidence for prevention of fractures with bisphosphonates is most clear for women with osteoporosis
• Fractures also occur in the much larger group of women with osteopenia
  – Whether bisphosphonates are efficacious in women with osteopenia is unknown
• Focus on interventions decisions being based on absolute risk
  – Osteopenia in combination with other risk factors

The News

• Fracture Prevention with Zoledronate in Older Women with Osteopenia.
  – IR Reid et al. NEJM Dec, 2018.
• AIM: To determine the impact of zoledronate vs placebo on fracture risk in women aged 65 and older with osteopenia
Methods

- 2000 women age 65 and older with osteopenia
  - T score -1.0 to -2.5 at hip or femoral neck
- Zoledronate 5 mg or placebo at 18 month intervals
  - 4 doses
- Dietary calcium of 1 g or more a day advised
- Cholecalciferol before trial began and monthly during trial
- Outcome: First occurrence of nonvertebral or vertebral fragility fracture

Results

- Participant characteristics
  - Average age 71.5
  - Average t score -1.6 ±0.5
  - Median 10 year risk of hip fracture 2.3%
- Fragility fractures
  - 190 placebo vs 122 zoledronate: HR 0.63 (0.50,0.79)
  - NNT to prevent one fracture: 15
- Zoledronate treated women also had lower risk of nonvertebral fragility fractures, vertebral fractures and height loss
- No impact on hip fracture
  - HR 0.66 (0.27,1.16)
Limitations

• Dosing regimen is different from what we typically use
• Reduction in fragility fractures but no reduction in hip fracture, which is the most clinically significant outcome
• Some included women had osteoporosis in one hip and osteopenia in the other
  – Higher risk group

Conclusion

• Risk of nonvertebral or vertebral fragility fractures significantly lower in women with osteopenia who received zoledronate than who received placebo
Impact for Practice

• Treatment of many women over 65 with osteopenia could prevent future fractures
• Future research should target identifying those women with osteopenia most likely to benefit from treatment.
• In the interim, for Bea, consider the FRAX tool to calculate her risk
  – However no clear benefit on hip fracture reduction will limit use for now

Quick Take: FDA approval

• Romosozumab (sclerostin inhibitor) shown last year in ARCH trial to be associated with a reduction in clinical and vertebral fracture among women with osteoporosis and a fragility fracture
• Treatment was for one year followed by alendronate
• Warning about increased risk of MI, stroke and CV death
• Romosozumab is now FDA approved for use for one year for postmenopausal women at high fracture risk or in whom other treatments have failed
  – Monthly subcutaneous injection
Violet Dee

• Violet Dee is a 67 year old woman who has been taking supplemental Vitamin D at your recommendation. When you tell her that she is due for her mammogram, she asks “Why do I need a mammogram if I am taking Vitamin D? I heard that vitamin D prevents cancer.”
• What do you tell Violet?

Vitamin D: What do you tell Violet?

• Vitamin D has been shown to reduce breast cancer risk
• Vitamin D decreases the risk of heart disease, but not cancer
• Vitamin D is only good for your bones
• Vitamin D treatment helps to improve fatigue
Vitamin D

“Good for all that ails you!”

Background

• Vitamin D important for bone health but its impact on other health outcomes is less clear
• In primary care practice, testing Vitamin D levels and prescribing Vitamin D supplements is very common
• Little is known about the impact of Vitamin D supplementation on cancer and cardiovascular disease
The News

• Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease
  – JA Manson et al. NEJM January, 2019

• AIM: To determine the impact of daily Vitamin D supplementation on prevention of cardiovascular disease and cancer

Methods

• 2 x 2 factorial design
  – Vitamin D 2000 IU daily vs placebo
  – Omega 3 fatty acids vs placebo

• US Dwelling men aged 50 and older and women aged 55 and older
  – No history of cancer or cardiovascular disease at baseline

• Primary Outcomes: Invasive cancer of any type and major cardiovascular outcomes
  – Secondary outcomes: site specific cancers, cancer death and other cardiovascular outcomes
Results

- 25,871 participants
  - 13,085 women (51%)
- Median 5.3 year follow up
- Mean 25-OH Vitamin D at baseline 30.8±10 ng/ml
- At follow up in subset, 25-OH Vit D increased by 40% in Vitamin D group
- Adherence over 80%

Results

- Cancer diagnosed in 793 participants in Vitamin D group and 824 in the placebo group
  - HR 0.96 (0.88,1.06)
- No difference in major cardiovascular events
  - 396 in Vitamin D group vs 409
  - HR 0.97 (0.85,1.12)
- No differences in secondary endpoints
  - Cancer mortality, breast cancer, CRC
Results

- No decrease in invasive cancer of any type in women
  - HR 1.02 (0.87, 1.18)
- No decrease in major cardiovascular events in women
  - HR 0.93 (0.76, 1.14)
- No increased hypercalcemia or other adverse events

Limitations

- Follow-up only 5.3 years
- Only one dose of Vitamin D
Conclusions

• Vitamin D supplementation did not result in a lower incidence of invasive cancer or cardiovascular events.

Impact for Practice

• Vitamin D is important for bone health but no evidence that it should be prescribed to reduce cancer or cardiovascular disease risk
• Violet still needs a mammogram
USPSTF: Interventions to Prevent Falls

- Update of 2012 guidelines to prevent falls in community dwelling older adults
- Evaluation of effectiveness of primary care relevant interventions to prevent falls
- Exercise interventions to prevent falls in community dwelling adults age 65 and older who are at increased risk of falls (B)
- Selectively offer multifactorial interventions to prevent falls (C)
- Recommends against Vitamin D supplementation to prevent falls (D)
  - USPSTF, April 2018

USPSTF: Fracture Prevention

- Update of 2013 recommendations – (but no change!)
- Recommends against supplementation with 400 IU or less of Vitamin D and 1000 mg calcium or less for primary prevention of fractures (D)
- Evidence insufficient to assess balance of benefits and harms of daily supplementation with doses >400 IU of Vitamin D and >1000 mg calcium for primary prevention of fracture in community dwelling postmenopausal women (I)
  - USPSTF 2018
USPSTF
Screening for Vitamin D Deficiency

• Should we be screening for Vitamin D deficiency?
• USPSTF concludes that the evidence is insufficient to assess the balance of benefits and harms of screening for Vitamin D deficiency in asymptomatic adults

Summary: Vitamin D

• Ensure adequate intake of Vitamin D
  – 600-800 IU daily
• Population wide screening for 25-OH Vitamin D deficiency not recommended
• Vitamin D supplementation is not recommended for cancer or cardiovascular disease prevention
Kate

- Kate is a 53 year old woman who has just been treated for hormone sensitive breast cancer. She has been taking exemestane for several months but is very bothered by the joint pain. Tylenol does not help and NSAIDs cause her an upset stomach. She is wondering if there are any other alternatives for the pain.
What do you tell Kate?

• Keep taking the NSAIDs. We will add a medication (PPI) to protect your stomach)
• Why don’t you try taking the tylenol more often?
• Do you want to try acupuncture?
• Don’t worry. It will go away when you stop the exemestane.

Background

• Aromatase inhibitors (AI) have efficacy in treatment of hormone sensitive breast cancer
• Arthralgias can occur in about 50% of patients
• Acupuncture involves insertion of needles into certain meridians and is a nonpharmacologic modality used to treat many conditions
• Prior studies of the impact of acupuncture on AI related arthralgias have been small not well blinded, single center studies
The News

• Effect of acupuncture vs sham acupuncture or wait list control on joint pain related to aromatase inhibitors among women with early stage breast cancer: a randomized clinical trial
  – Hershman et al. JAMA 2018

• AIM: To determine the impact of acupuncture on AI related joint pain

Methods

• RCT in 11 US centers
• Participants: Postmenopausal women with early stage breast cancer who were taking AI, scored at least 3 on Brief Pain Inventory Worst Pain (BPI-WP) Item
  – BPI-WP range 0-10
• Intervention: Acupuncture, sham acupuncture, wait list control
• Acupuncture was twice a week for 6 weeks, then once a week for 6 weeks
• Sham acupuncture used thin short needles inserted to shallow level not at acupuncture point
Results: Participant Characteristics

- 226 randomized
  - 110 acupuncture
  - 59 sham
  - 57 wait list
- Mean age 60.7
- 88% white
- 91% completed trial

Results

- Mean BPI-WP score decreased more in acupuncture group
  - 2.05 point reduction in true acupuncture group
  - 1.07 in sham acupuncture group
  - 0.99 in wait list control
- Adjusted difference true acupuncture vs sham
  - 0.92 (0.2,1.65: P=0.01)
- Adjusted difference true acupuncture vs wait list
  - 0.96 (0.24,1.67: p=0.01)
- More grade 1 bruising in true acupuncture group
Limitations

• Clinical significance of the differences in BPI-WP scale unclear
• Sham acupuncture performed by same people as did the true acupuncture
  – They knew it was sham

Conclusion

• In postmenopausal women with early stage breast cancer and aromatase inhibitor related arthralgias, acupuncture resulted in a reduction in pain as measured by the BPI-WP scale, although the clinical significance is unclear.
Impact for practice

• Acupuncture may have the potential to be a nonpharmacologic addition to treatment for AI associated joint pain
  – No significant harms and chance of benefit

UTIS and Incontinence
Susan

Otherwise healthy 35yo who presents to your office with her 4th UTI in the past year. In the past, you’ve prescribed nitrofurantoin. She asks if, this time, you would consider prescribing the same one-dose antibiotic she received in urgent care last month. She also wants to know what she can do to reduce her frequency of UTIs.

What should you prescribe?

- Single dose fosfomycin
- Nitrofurantoin for a 5 day course
- Don’t prescribe anything. A lot of UTIs will get better on their own anyway.
Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomized Clinical Trial.

Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections: A Randomized Clinical Trial.

Nitrofurantoin vs. Single dose Fosfomycin

Study Rationale
• 2010 IDSA guidelines incorporated nitrofurantoin and fosfomycin as first line agents
  – Use of these antimicrobial regimens has increased
• Existing clinical efficacy data supporting the use of single-dose fosfomycin is not as robust

Question: In women with uncomplicated UTI, what is the clinical and microbiologic efficacy of nitrofurantoin and fosfomycin?
Nitrofurantoin vs. Single dose Fosfomycin

Population: 513 women with >1 symptom of UTI and a positive dipstick
- Excluded: complicated UTI, renal insufficiency, immunosuppression, recent antibiotics

Intervention: fosfomycin 3g PO x 1 dose
Comparison: nitrofurantoin 100mg PO TID x 5 days*

Outcomes: Clinical response at 28 days
- Secondary outcomes: microbiological resolution, duration of symptoms, pyelonephritis, urosepsis, clinical/microbiological resolution at 14 days

Type: RCT in 1:1 ratio, 95% ITT analysis

UTI Symptoms
- Dysuria
- Urgency
- Frequency
- Suprapubic Tenderness

Positive Dipstick
- Nitrates
- Leukocyte Esterase

Nitrofurantoin vs. Single dose Fosfomycin

Clinical Resolution
- Nitrofurantoin: 171/244 (70%)
- Fosfomycin: 139/241 (58%)
- Absolute difference 12% [95%CI 4-21%], p = 0.004

Microbiological resolution
- Nitrofurantoin: 129/175 (74%)
- Fosfomycin: 103/163 (63%)
- Absolute difference 11% [95%CI 1-20%], p = 0.04

No difference in
- Duration of symptoms: 4d vs. 3d, nitrofurantoin vs. fosfomycin, p=.30
- Occurrence of pyelonephritis: 0.4% vs. 2%, p=0.22

No urosepsis or other serious adverse events
Impact

• A 5d course of nitrofurantoin has higher clinical and microbiological resolution of uncomplicated UTI in women than does single-dose Fosfomycin, at 28 days

Given similar rates of AEs and higher rates of cure for nitrofurantoin, these results will lower my likelihood of prescribing Fosfomycin for cystitis in women

Water intake

• Many informal recommendations support water intake as a positive health practice
• “8 Glasses a day”
• What is the evidence for an impact of water intake on health outcomes?
Effect of Increased Water Intake on Recurrent UTI

Question: In premenopausal women with a history of recurrent cystitis, does increased daily water intake reduce the risk for recurrence?

- **Population:** 140 premenopausal women with recurrent cystitis in the setting of low fluid intake and the absence of current UTI sx
- **Intervention:** 1.5L water per day in addition to usual fluid intake
- **Comparison:** Usual fluid intake
- **Outcomes:** Frequency of recurrent cystitis in 1y
  - Secondary: number of antimicrobial regimens used, time between episodes, and number of voids/day
- **Type:** RCT in 1:1 ratio

<table>
<thead>
<tr>
<th></th>
<th>Increased water</th>
<th>Usual fluid intake</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean water intake</strong></td>
<td>+1.7 Liters</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td><strong>Mean No. cystitis episodes</strong></td>
<td>1.7</td>
<td>3.2</td>
<td>1.5, 95% CI [1.2-1.8]</td>
</tr>
<tr>
<td><strong>Mean No. antimicrobial regimens</strong></td>
<td>1.9</td>
<td>3.6</td>
<td>1.7, 95% CI [1.3-2.1]</td>
</tr>
<tr>
<td><strong>Mean time between episodes</strong></td>
<td>143 days</td>
<td>84 days</td>
<td>58 days, 95% CI [39-77]</td>
</tr>
<tr>
<td><strong>Mean No. voids/day</strong></td>
<td>8.2</td>
<td>5.9</td>
<td>2.3, 95% CI [1.825, 2.775]</td>
</tr>
</tbody>
</table>
Impact:

Increased water intake is an effective antimicrobial sparing strategy in premenopausal women with recurrent uncomplicated UTI

- 50% reduction in frequency of cystitis recurrence
- Similar reduction in antimicrobial prescription

It is SAFE and INEXPENSIVE

- Though may worsen symptoms in women with OAB

Dolores

A 63yo post-menopausal woman who mentions during a routine visit that she is having urine leakage with coughing and also urgency that sometimes causes her to lose urine before reaching the toilet. She asks you what the most effective treatment for her symptoms would be.
What do you tell Dolores?

- Behavior treatment including bladder training and muscle strengthening
- Anti-cholinergics
- Systemic or topical hormone therapy
- Neuro-modulation therapy

Urinary Incontinence Treatments

- Behavioral: bladder training, biofeedback, bladder support (including pessaries), weight loss, yoga
- Neuromodulation: electroacupuncture, sacral neuromodulation, TENS, magnetic stimulation
- Hormones: (vaginal or systemic)
- Periurethral bulking
- Alpha agonists for stress incontinence
- Anti-cholinergics for urge incontinence
- Anti-epileptics for urge incontinence
- Beta adrenergic agonists for urge incontinence

Quick take!

**Question:** Comparative effectiveness of pharmacologic and behavioral interventions for incontinence?

**IMPACT**
- Most interventions were more effective than no treatment in terms of symptom improvement or resolution
- Behavioral therapy interventions (alone or combined) were more effective for all types of incontinence
  - Stress UI: behavioral therapy >> α agonists >> hormones
  - Urge UI: behavioral therapy >> anticholinergics
- Limitations: few head-to-head trials, high heterogeneity

- Behavioral: broad category that focuses on bladder training and muscle strengthening
- Neuromodulation: both electrical and magnetic stimulation
- Hormones: estrogen, raloxifene, various routes
- Anticholinergics: 11 drugs
- Intravesical pressure release
- Botox
- Periurethral bulking
Urinary Incontinence Treatments

- Start with behavioral therapies
- Medications less effective and high rate of discontinuation due to side effects
- Behavioral therapies alone or in combination with other interventions more effective than pharmacotherapy alone for stress and urge incontinence

Laila

A 54-year old woman, presents to you for evaluation of hot flashes. She is having difficulty sleeping at night due to these & wonders if hormone therapy would be right for her. However, she is worried because her best friend was recently diagnosed with a DVT after starting hormone therapy. She is confused about how this will affect her risk for VTE.
What do you tell her?

• There is a small risk of DVT with hormone therapy- but just because your best friend had it, does not mean that you will
• If you are going to take hormone therapy, the transdermal method is probably safest.
• Nobody uses hormone therapy any more- let’s try venlafaxine instead
• Why don’t you just try black cohosh?

Background

• Menopausal symptoms are distressing for many women
  — ...and can last a long time!
• We have many nonpharmacologic alternatives
  — But hormone therapy works best!
• Decision making about appropriate use of hormone therapy is complicated
  — “Lowest dose for shortest duration”
The News

Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the Qresearch and CPRD databases.


Use of HT and risk of VTE

Question: Are some types of HT lower risk for VTE than others?

- **Population:** ~80000 women 40-79yo with a primary diagnosis of VTE
- **Intervention:** hormone therapy
- **Comparison:** 391,000 controls matched by age, practice location and index date
  - OR adjusted for demographics, smoking, alcohol, comorbidities, recent medical events
- **Outcome:** VTE
  - Subgroup analysis: Age and BMI categories
- **Type:** Nested case-control studies from 2 large UK primary care databases

**Timing**
- Recent (within 90d of index date)
- Past (91-365 days from index date)
- None
**Type of estrogen and progesterone**
- Oral HT (included both E and E+P)
- Transdermal HT

**Dosage**
- Low: ≤ 0.625mg oral CEE, ≤ 1 mg oral estradiol, ≤ 50mcg transdermal estradiol
- High

**Duration of exposure**
- Short term ≤ 90 days
- Long term > 90 days
**Use of HT and risk of VTE**

**Compared to no HT exposure**

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<tr>
<th>HT Type</th>
<th>Combined Analysis Odds Ratio (95% CI)</th>
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<tr>
<td>Any HT</td>
<td>1.43 (1.38 to 1.48)</td>
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<tr>
<td>Oral preparations</td>
<td>1.58 (1.52 to 1.64)</td>
</tr>
<tr>
<td>• CEE alone</td>
<td>1.49 (1.39 to 1.60)</td>
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<tr>
<td>• E2 alone</td>
<td>1.27 (1.16 to 1.39)</td>
</tr>
<tr>
<td>• CEE combined</td>
<td>1.91 (1.79 to 2.05)</td>
</tr>
<tr>
<td>• E2 combined</td>
<td>1.59 (1.49 to 1.69)</td>
</tr>
<tr>
<td>Transdermal preparations</td>
<td>0.93 (0.87 to 1.01)</td>
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Use of HT and risk of VTE

**Compared to no HT exposure**

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**DIRECT comparison between types of HT**

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<thead>
<tr>
<th>HT Comparison</th>
<th>Combined Analysis Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral v transdermal</td>
<td>1.70 (1.56 to 1.85)</td>
</tr>
<tr>
<td>E2 only v CEE only</td>
<td>0.85 (0.76 to 0.95)</td>
</tr>
<tr>
<td>E2 combined v CEE combined</td>
<td>0.83 (0.76 to 0.91)</td>
</tr>
</tbody>
</table>

• Higher doses = higher risks
• Results were consistent with main analysis across BMI and age subgroups

**IMPACT**

• Transdermal treatment is the safest mode of HT with respect to VTE
• For women or transgender individuals with any baseline risk factors for VTE (e.g., obesity), would recommend transdermal rather than oral estrogen
• For menopausal women with indications for oral estrogen (either alone or combined), would consider estradiol as opposed to CEE
Pamela

Pamela is 27yo woman, otherwise healthy, and has been using extended cycle OCPs due to cyclic menstrual symptoms. She presents to your office because she talked to Laila and she is concerned about her risk for VTE.

The News

Association of risk for VTE with use of low-dose extended- and continuous-cycle COCs: A safety study using the sentinel distributed database.
- Li et al. JAMA Intern Med. 2018, November
Quick take!

Question: Is the risk for VTE higher with use of continuous (84/7) or extended (365/0) COCs than cyclic COCs among initiators?

IMPACT

• Overall HR of VTE 1.32, 95% CI [1.07-1.64] for continuous/extended
  – Non-cyclic incidence rate 1.44/1000 person-years
  – Cyclic incidence rate 1.09/1000 person-years
  – Absolute risk difference 0.27 per 1000 persons

Extended-cycle COCs are an acceptable option in patients with cyclic menstrual symptoms

Pregnancy-Associated Health
Jessie

Jessie Pain is a 53 y/o woman who presents for annual exam. She has hypertension controlled on chlorthalidone and wonders if she should take a statin.

What additional history is needed to answer this question?
ACC/AHA Lipid Update

“In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy.”

• Risk-enhancing factors include:
  – history of premature menopause (before age 40 years) and
  – history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia

Grundy SM et al. JACC

Circulation: Pregnancy-associated CV Risk Factors

Question: Which complications of pregnancy increase risk of CVD in women?

Study Type: Systematic review of cohort and case-control studies

Grandi et al. Circulation February 2019
Pregnancy-associated CV Risk Factors

- Population: 28,993,438 women who had experienced pregnancy
- Exposure: selected complications of pregnancy
- Controls: no complications
- Outcomes: development of cardiovascular disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Increased future CVD risk</th>
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<tbody>
<tr>
<td>Gestational HTN</td>
<td>Yes</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>Yes</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Yes</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>Yes</td>
</tr>
<tr>
<td>Gestational DM</td>
<td>Yes</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>Yes</td>
</tr>
<tr>
<td>Low birth weight or SGA birth weight</td>
<td>Trend toward yes</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>Unable to pool studies due to heterogeneity</td>
</tr>
</tbody>
</table>

Grandi et al. Circulation February 2019

PERINATAL DEPRESSION
The News:

• Interventions to Prevent Perinatal Depression Evidence Report and Systematic Review for the US Preventive Services Task Force
  — O’Connor et al. JAMA Feb 2019

• Interventions to Prevent Perinatal Depression US Preventive Services Task Force Recommendation Statement
  — USPSTF JAMA Feb 2019

• Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials
  — Meltzer-Brody et al Lancet August 2018

Anna is a 29 year-old woman who presents to primary care at 25 weeks gestational age. She read that she is at increased risk of perinatal depression due to her history of depression and wonders if there is anything she can do now to help prevent recurrence?
USPSTF: Interventions to Prevent Perinatal Depression

Questions:
1. Do interventions to prevent perinatal depression improve health outcomes?
2. What harms are associated with interventions to prevent perinatal depression?

Population: 22,385 pregnant and postpartum women
Interventions: counseling, health system interventions, physical activity, peer counseling, SSRIs, nortriptyline, omega-3 fatty acids
Outcome: Reduction in postpartum depression
Study Type: Systematic review (50 trials)

Who did studies identify as high risk?

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal or family history of depression</td>
</tr>
<tr>
<td>Elevated depressive symptoms</td>
</tr>
<tr>
<td>Socioeconomic factors</td>
</tr>
<tr>
<td>Young age</td>
</tr>
<tr>
<td>Recent intimate partner violence</td>
</tr>
<tr>
<td>Other mental health concerns (i.e. anxiety symptoms)</td>
</tr>
<tr>
<td>Recent significant negative life events</td>
</tr>
</tbody>
</table>

USPSTF JAMA Feb 2019
Perinatal Depression Prevention: Results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Counseling:</strong></td>
<td></td>
</tr>
<tr>
<td>CBT or IPT in particular</td>
<td>Pooled risk ratio 0.60, 95% CI 0.43-0.83</td>
</tr>
<tr>
<td></td>
<td><strong>Number needed to treat =13.5</strong></td>
</tr>
<tr>
<td><strong>Medications:</strong></td>
<td></td>
</tr>
<tr>
<td>Sertraline, 1 study, n=22</td>
<td>Reduction in depression at 20 weeks postpartum</td>
</tr>
<tr>
<td></td>
<td>Increased side effects (somnolence, dizziness)</td>
</tr>
<tr>
<td><strong>Other interventions:</strong></td>
<td></td>
</tr>
<tr>
<td>Physical activity, infant sleep education, in-hospital perinatal education, peer counseling, health system interventions (i.e. navigation, screening)</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>

USPSTF JAMA Feb 2019

Perinatal Depression Prevention

- **Strengths**
  - Clinically important research question
  - First major scoping review to address this topic

- **Limitations**
  - Significant variability in outcomes for non-counseling interventions
  - Few trials assessed pharmacologic benefits or harms and these were very small trials
  - Risk for depression was variably assessed prior to interventions

**USPSTF Recommendation (B recommendation)**
- Provide or refer persons at increased-risk of perinatal depression to counseling interventions [CBT or IPT]
Quick take: Brexanolone

- Synthetic allopregnanolone,
  - endogenous progesterone metabolite
  - decreases considerably following childbirth
  - an association between its fluctuations and postpartum depression had been posited
- Neuro-steroid, positive modulator of GABA-A receptors

Meltzer-Brody et al  Lancet August 2018

---

Quick take: Brexanolone

- Efficacy: improvement in depression scores by 24 hours, sustained response at 7 days, 30 days.
- Side effects: headache, dizziness, pre/syncope, somnolence
- Requires 60-hour inpatient infusion
- Study required patients to forgo breastfeeding during infusion and for 4 days following infusion
- Estimated cost >$20,000/treatment

Impact:
- First FDA approved medication for post-partum depression
- Only available in certified centers (June 2019)
- Cost and logistics to administer will likely limit use

Meltzer-Brody et al  Lancet August 2018
CERVICAL CANCER SCREENING

The News:

• Effect of Screening with Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 months: the HPV FOCAL Randomized Controlled Trial
  – Ogilvie et al. JAMA Feb 2019

• Primary cervical screening with hrHPV testing: observational study
  – Rebolj et al. BMJ Feb 2019

• Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement
  – US Preventive Services Task Force JAMA Aug 2018
Natalie is a 32 year-old woman who presents for annual physical. Her most recent pap smear was 3 years ago and was normal. She asks if she is due for her pap today.

What do you say?

---

**HPV FOCAL Randomized Controlled Trial**

- **Population:** 19,009 Canadian women participating in the organized Cervical Cancer Screening Program, ages 25-65 (average 45)
- **Intervention:** Primary hrHPV screening, reflex liquid-based cytology
- **Control:** Liquid-based cytology with reflex hrHPV screening
- **Outcomes:**
  - Primary: Cumulative incidence of CIN 3+ at 48 months
  - Secondary: Cumulative incidence of CIN 2+ at 48 months

Ogilvie et al. JAMA Feb 2019
HPV FOCAL Trial: Study Design

Baseline Testing
- 9540 completed baseline hrHPV
- 9408 completed baseline LBC
- 8769 HPV- (return at 48 months)
- 771 HPV+ (reflex testing protocol)
- 9074 negative cytology (return at 24 months)
- 334 + cytology (reflex testing protocol)

24 Month Follow-up (LBC Arm Only)
- 7994 completed 24 month f/u testing
- 7808 cytology negative (return at 48 months)
- 185 + cytology (reflex testing protocol)

48 Month Follow-up
- 8296 returned for 48 month f/u
- 8078 returned for 48 month f/u testing

HPV FOCAL Trial: Results

1. All participants at 48-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>HPV testing Incidence/1000 (95% CI)</th>
<th>LBC testing Incidence/1000 (95% CI)</th>
<th>Absolute difference HPV-LBC (95% CI)</th>
<th>Risk Ratio (95% CI) HPV vs LBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 3+</td>
<td>2.3 (1.5-3.5)</td>
<td>5.5 (4.2-7.2)</td>
<td>-3.22 (-5.12 to -1.48)</td>
<td>0.42 (0.25-0.69)</td>
</tr>
<tr>
<td>CIN 2+</td>
<td>5.0 (3.8-6.7)</td>
<td>10.6 (8.7-12.0)</td>
<td>-5.6 (-8.21 to -3.31)</td>
<td>0.47 (0.34-0.67)</td>
</tr>
</tbody>
</table>

2. Participants with baseline negative results, at 48-month follow-up

<table>
<thead>
<tr>
<th></th>
<th>HPV testing Incidence/1000 (95% CI)</th>
<th>LBC testing Incidence/1000 (95% CI)</th>
<th>Absolute difference HPV-LBC (95% CI)</th>
<th>Risk Ratio (95% CI) HPV vs LBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 3+</td>
<td>1.4 (0.8-2.4)</td>
<td>5.4 (4.1-7.1)</td>
<td>-4.03 (-5.88 to -2.41)</td>
<td>0.25 (0.13-0.48)</td>
</tr>
<tr>
<td>CIN 2+</td>
<td>3.6 (2.6-5.1)</td>
<td>10.8 (8.2-12.3)</td>
<td>-7.2 (-9.89 to -4.02)</td>
<td>0.36 (0.24-0.54)</td>
</tr>
</tbody>
</table>

Ogilvie et al. JAMA Feb 2019
HPV FOCAL Trial: Results

3. Colposcopy referral rates

<table>
<thead>
<tr>
<th></th>
<th>HPV testing Incidence/1000 (95% CI)</th>
<th>LBC testing Incidence/1000 (95% CI)</th>
<th>Absolute difference HPV-LBC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>57 (52-61.9)</td>
<td>30.8 (27.5-34.5)</td>
<td>26.2 (20.4-32.1)</td>
</tr>
<tr>
<td>48 month f/u</td>
<td>49.2 (45-53.7)</td>
<td>70.5 (65.5-75.8)</td>
<td>-21.3 (-28.3 to -14.8)</td>
</tr>
</tbody>
</table>

Ogilvie et al. JAMA Feb 2019

HPV FOCAL Randomized Controlled Trial

**Strengths**
- Large, population based randomized controlled trial
- Standardized protocols and laboratory testing to reduce bias
- Standardized colposcopy procedures

**Limitations**
- Single country study with nationalized cervical cancer screening program may not be replicable elsewhere
- Cohort was highly educated and largely from 2 geographic regions; underrepresented rural and remote populations

**Conclusions:**
1. Patient screened with primary hrHPV had less CIN 3+ or CIN 2+ on 48-month testing.
2. The increase in colposcopy during baseline testing did not persist at 48 month testing.

Ogilvie et al. JAMA Feb 2019
## USPSTF Update: Cervical Cancer Screening

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
<th>Considerations</th>
<th>Cervical Cancer Deaths*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>20-29</strong></td>
<td>Every 3 years</td>
<td>• High rates of cleared hrHPV in this age group, thus cytology preferred to avoid risk of overtreatment</td>
<td></td>
</tr>
<tr>
<td><strong>30-65</strong></td>
<td>Every 3 years</td>
<td>• Lower sensitivity than primary hrHPV&lt;br&gt;• Lower false-positive rate &amp; rate of additional testing</td>
<td>0.76 per 1000 women</td>
</tr>
<tr>
<td></td>
<td>Every 5 years</td>
<td>• 4 RCTs demonstrate adequate sensitivity&lt;br&gt;• Follow protocols for reflex testing with + result</td>
<td>0.29 per 1000 women</td>
</tr>
<tr>
<td></td>
<td>Every 5 years</td>
<td>• May detect slightly more cases of CIN than hrHPV&lt;br&gt;• Significant increase in the number of tests and procedures</td>
<td>0.30 per 1000 women</td>
</tr>
</tbody>
</table>

*8.34 per 1000 women die without screening

## Thyroid Disease
Tracy

48 yo Hx of Hashimoto’s on thyroid replacement therapy
Here to follow up on chronic fatigue.
Recent normal TSH, free T4, CBC, lytes
(as it has been since you met her 2 years ago)

Anything new to consider?

What do you suggest

• Increase the levothyroxine dose a little to keep TSH in low normal range
• Add cytomel (T3)
• Administer a PHQ 9
• Refer her for thyroidectomy
The News:

• Thyroidectomy versus medical management for euthyroid patients with Hashimoto disease and persisting symptoms: A randomized trial.

Methods

Randomized
• 150 euthyroid Norwegians (137 women)
• Persistent Hashimoto-related symptoms
• Anti-TPO Ab titers >1000 IU/mL
• Aged 18–79

• Followed for 18 months
• after thyroidectomy plus Standard medical therapy
  OR
  Standard medical therapy
Results

- Postop, anti-TPO antibody titers rapidly dropped & were normal in almost all by 18 months.
- **Chronic fatigue dropped from 82% to 35%** with improved quality of life

Take home

- Consider referring patients for thyroidectomy if they remain symptomatic despite medical management for Hashimoto’s disease and evaluation of other contributing causes
Female Sexual Dysfunction

• Lack of sexual desire
• Impaired arousal
• Inability to achieve orgasm
• Pain with sexual activity
• Combinations of issues
Approach: Multifactorial

- Counseling
- Lifestyle Changes
- Improving Body Image
- Treating pelvic floor dysfunction
- Medications
  - Hormones
  - Serotonergic or dopaminergic agents

Testosterone

- Typically used for issues of sexual desire
- Transdermal testosterone 300 mcg/day for 6 months is safe and effective in women receiving estrogen therapy
  - One study of women not receiving concurrent estrogen
    - 300 mcg group had more side effects
    - 150 and 300 mcg group had similar improvements in desire
Flibanserin

- Centrally acting serotonin receptor agonist/antagonist
  - Initially evaluated as anti-depressant and shown to increase sex drive
- FDA approved for female sexual interest/arousal disorder in 2015
- Small increases in sexual desire and sexually satisfying events
- Daily dose of 100 mg at bedtime
  - Black box warning hypotension and syncope
    - Increased with alcohol

The News: Bremelanotide

- Melanocortin receptor agonist FDA approved for HSDD in premenopausal women
- Administered as subcutaneous injection 45 minutes before anticipated sexual activity
- Increase in sexual desire (51% vs 21%) and sexual satisfaction (57% vs 26%)
  - No increase in SSE
    - Koochaki, 2019 and www.fda.gov
Bremelanotide

- Advantage: use when necessary
- Nausea common (40%)
  - 13% of women needed anti-emetics
- Transient blood pressure increases
- Fetal harm in animal studies
- Contraception

Take home

- Start with counseling, lifestyle changes, improving body image, treatment of pelvic floor dysfunction
- Medication options:
  - Testosterone
  - Flibanserin
  - Bremelanotide
- Premenopausal vs postmenopausal women
Summary

• Zoledronate shows some efficacy for women aged 65 and older with osteopenia
• Romosozumab now FDA approved for women at high risk for osteoporosis in whom other treatments have failed
• Acupuncture may be useful in treatment of AI related joint pain

Summary

• Nitrofurantoin appears to be superior to single dose fosfomycin for UTIs
• Increased water intake can reduce UTIs but may exacerbate overactive bladder
• Transdermal estrogen may be safer with respect to DVT risk
• Small increased DVT risk with continuous OCPs is unlikely to be of major clinical significance
Summary

• Consider additional pregnancy related risk factors in assessing cardiovascular risk
• Refer women at high risk for perinatal depression for counseling
• New cervical cancer screening recommendations include hrHPV alone as an option
• Consider thyroidectomy for women with persistent symptoms
• Bremelanotide is a new treatment for female sexual dysfunction

Questions?
Parkinson’s Disease and Tremors

Current Strategies

Leah Karliner, MD, MAS
Division of General Internal Medicine
University of California, San Francisco

Disclosures

• I have no conflicts of interest
Outline

• Parkinsonism
• Parkinson’s Disease
• Essential Tremor

Parkinsonism – neurological syndrome:

• Bradykinesia: (slow and reduced scale)
• Rest tremor: “pill rolling”
• Rigidity: resistance to passive movement
• Postural instability: falls, flexed posture
Parkinsonism Differential Diagnosis

- Neurodegenerative
  - Parkinson’s disease
  - Parkinson’s plus degenerative diseases
  - Mild parkinsonism in aging, AD, FTD
  - Other hereditary: e.g., Wilson’s disease, Huntington’s disease

- Acquired
  - Drug-induced parkinsonism
  - Structural lesions, trauma, vascular
  - Toxic: manganese, CO, cyanide, MPTP
  - Infections: (e.g. post encephalitic parkinsonism in early 20th century); HIV

Drug-induced Parkinsonism

- Neuroleptics
  - Less likely with atypicals (particularly quetiapine and clozapine)

- Anti-emetics
  - Prochlorperazine, metaclopramide

- Calcium-channel blockers - flunarizine

- Methyldopa

- Possibly – amiodarone, lithium
Drug-induced Parkinsonism

Epidemiology
- More common with aging
- More common among women
- May have a genetic predisposition

- Onset usually quick (50% within 1 month)
- Not progressive

Resolution after stopping the drug
- 60% resolve within 2 months (some almost immediately)
- Some take up to 2 years to resolve
- Some ‘unmasked’ idiopathic PD
Idiopathic Parkinson’s Disease

- Second most common neurodegenerative disease after Alzheimer’s Disease

- Approx 1.5 million in the US with Parkinson's disease

- About 50,000 new cases diagnosed each year in the US

- Mean age of onset 60 years
  - Prevalence 1% in >65 age; 2.5% in >80 age group
  - < 40 years is young onset (low prevalence)

- Cause is unknown, and there is presently no cure
  - 10-15% of cases may be familial
  - Possible gene-environment interaction in other cases

Pathophysiology

- Substantia nigra degenerates, results in dopamine deficiency in striatum and motor symptoms
Diagnosis

Clinical diagnosis, but *not* a diagnosis of exclusion

- Bradykinesia and at least of one the following:
  - Rest tremor
  - Rigidity
  - Postural Instability (later feature)

- Exclude use of dopamine blocking meds
- Exclude common metabolic problems: TSH, CA, CBC, lytes, hepatic dysfunction
- Observation of casual gait is highly informative
- Rest tremor is a great clue but is absent in 25% of cases
Diagnosis

Supportive criteria for PD diagnosis:
- Unilateral onset with asymmetry persisting
- Progressive symptoms
- Excellent response to levodopa
- Preclinical clues (constipation, anosmia, REM Behavior Disorder)

Ddx: Parkinson’s Plus Syndromes

- Early falls, apathy, or diplopia suggest
  - Progressive Supranuclear Palsy
- Postural hypotension, autonomic dysfunction, or cerebellar findings suggest
  - Multiple System Atrophy
- Significant cognitive impairment suggests
  - dementia with Lewy bodies
Initial Work-up

• MRI to exclude other disease processes (e.g., vascular, hydrocephalus)

• Screen for Vitamin B12 and supplement if <300pg/ml

• Screen for depression & anxiety
  – Often co-occur with early PD and should be treated
    • SSRI or SNRI first line therapy

Early Symptoms

The Michael J. Fox Foundation for Parkinson’s Research
https://www.youtube.com/watch?v=CqEwPqUO1Bw
Bradykinesia

- Paucity of movement
- Decreased amplitude of movement
- Micrographia
- Hypophonia
- Masked facies
- Reduced gesturing
- Reduced arm swing

PD Tremor

- Tremor at rest
- Often involves the thumb
- Typically slow 3-5 hertz tremor
- Improves with movement but can reemerge with sustained posture
Gait Abnormalities

Earlier signs/milder disease

• Small stride length
• Step changes/ dragging feet
• Stooped posture
• Reduced arm swing

Nicholas Galifianakis, MD UCSF
https://www.youtube.com/watch?v=F0cQuCYI4JM&list=PLD3FgfkwrzrEooQoZ6fFyKCIkcaWWftcMQ&index=3
Gait Abnormalities

Later signs

• Trouble initiating gait, changing directions, crossing thresholds
• Festinating gate - difficulty stopping (later sign)
• Postural instability (pull test)

Mild Cognitive Impairment

• 25-30% prevalence estimates; definitions have varied
• May be present even at early diagnosis
  – May not impact functioning
• Testing may demonstrate impairment in
  – Executive functioning (planning and executing tasks)
  – Attention difficulties (particularly in groups with multiple conversations)
  – Slowed thinking (time to complete tasks)
  – Word finding (due to slowed thinking, not loss of words)
  – Learning, organizing, and remembering new information
  – Imagery and spatial processing (making a mental picture)
Mild Cognitive Impairment

- Evaluation for other treatable causes
  - Vitamin B-12 deficiency
  - depression
  - fatigue
  - sleep disturbances

- PD does not cause acute fluctuation in cognition
  - Look for other cause, med effect, infection, etc.

PD Dementia

- Rate of progression to dementia remains unclear
  - Patients with PD have twice the rate of dementia compared to general pop

- Treatment in mild-moderate PD dementia (MMSE 10-24)
  - Rivastigmine 3-12mg
    - Improvements in language, memory, and praxis

Schmitt, Am J of AD & Other Dementias 2010
Initiating Treatment for Motor Symptoms

• No disease modifying therapy is available
• Delay pharmacologic treatment until symptoms interfere with function (work or social)
• Start with physical therapy, followed by development of exercise routine
• Pharmacologic therapy is aimed at dopamine replacement or preservation

Exercise

• Engagement in regular cardiovascular exercise improves fitness and walking performance
• Engagement in balance exercise decreases falls

- LI, NEJM 2012; Uhrbrand, J of the Neurological Sciences 2015; National Parkinson's Foundation: Fitness Counts; http://www.parkinson.org/Improving-Care/Education/Education--For-Patients/NPF-Literature

• Clinical Implication:
  – Goal: 150 min/week of cardiovascular exercise
    – Exercise walking, swimming, stationary bike, elliptical, etc.
  – Regular balance exercise
    – Yoga, Tai chi, dance
Treatment: PD Medication trial

- Pragmatic RCT of newly diagnosed PD patients
- Levodopa-sparing therapy (dopamine agonist or MAO-BI) vs. levodopa
- 1620 patients followed for median 3-years
- Outcomes:
  - Mobility and QOL

PD MED Collaborative Group; The Lancet 2014
• Improvements in both groups in mobility score; average difference favors levodopa

• No difference in summary score: mobility, ADLs, emotional well-being, stigma, social support, cognition, communication, bodily discomfort

• Levodopa with higher risk of dyskinesia earlier;

• Risk similar over time
Treatment

- Carbidopa-levodopa (Sinemet) – high potency, reliable, quick onset
  - most efficacious treatment for motor symptoms of PD
  - ‘on-off’ phenomenon and dyskinesias develop at rate of 10% annually for older patients, but more rapidly for younger patients
  - First line therapy for ≥ 65 years old
  - Carbidopa prevents peripheral conversion of levodopa to dopamine allowing for lower effective doses that may last longer

Treatment: Carbidopa-levodopa continued

- 3x daily dosing at least 1 hour before meals
- Can add COMT inhibitor (entacapone, tolcapone) for better bioavailability of levodopa & duration of effect
- Protein: competes with amino acids to cross the blood-brain barrier, will decrease clinical efficacy if taken with protein load

- Common side effects
  - Nausea
  - Abnormal dreams
  - Headache
  - Insomnia
  - Dyskinesias

- Less common
  - Orthostatic hypotension
  - Psychosis
  - Depression
  - GI bleeding
  - Sudden sleep episodes
Treatment: levodopa sparing

• MAO-B inhibitors: mild potency
  – Selegiline, rasagiline
    • Delay need for levodopa for a few months on average
    • Risk of serotonin syndrome; monitor when taking SSRI
    • At high doses inhibit MAO-A; avoid tyramine

• Dopamine agonists, non-ergot: moderate potency
  – Pramipexole, Ropinirole, Rotigotine
    • Decreased motor fluctuations compared with levodopa
    • Impulse control disorders (e.g., compulsive gambling, snacking, sexual interests, video games), daytime sleepiness, insomnia all common (10-20%)

https://youtu.be/koL0PWCJ4Io
Dyskinesias

- Involuntary choreiform and dystonic movements
- 30-40% of patients develop dyskinesia
- Rates appear similar for MAO-BIs and dopamine agonists
- Patients on levodopa may develop them earlier

Risk factors for dyskinesia development:
- Younger age of onset
- Increasing disease severity
- Higher levodopa dosage
- Longer disease duration

Dyskinesia Treatment

- If dyskinesia mild and not bothersome to patient – no treatment

- Bothersome / interfering with function
  - treat with amantadine
Treatment Escalation

- Approach to patient with wearing off phenomenon
  - Increase levodopa dose or frequency of dosing
  - If dyskinesias then develop, or duration of effect too short:
    - add dopamine agonist or COMT
    - lower the levodopa dose
  - Consider deep brain stimulation
Deep Brain Stimulation

- Best for patients with on-off phenomenon despite maximal oral therapy
- Patients must still have some benefit from levodopa, good cognition, good general health
- Expected benefits
  - Increased ‘on’ time
  - Reduced dyskinesias
  - Lower/fewer medications
- Risks
  - 2% peri-operative hemorrhagic stroke risk
  - 4% infection risk

Parkinson’s Hallucinations

- New medication FDA approved: Nuplazid
- Use alone or in combo with
  - cholinesterase inhibitors (Aricept)
  - or antipsychotics with low D2 antagonism (clozapine and quetiapine)
**Possible Future Treatments**

- infused antibodies against alpha synuclein
  - Protein found at presynaptic terminals in brain
- drugs to affect the activity of enzymes thought to be relevant to PD pathogenesis

**When to Refer to a Neurologist**

- Around time of diagnosis
- Poor response to medications
- Cognitive complaints
- Hallucinations
- Dysphagia
- Falls
What type of movement disorder is this?

[Video URL: https://youtu.be/nNQAFm2OYXQ]

What type of Movement Disorder is this?

1. Parkinson’s tremor
2. Chorea
3. Essential tremor
4. Dyskinesia
Essential Tremor

- Prevalence: 1-6% of population
- Onset peaks in 2\textsuperscript{nd} and 6\textsuperscript{th} decades
- Women and men equally affected
- 50-70% have a family history of essential tremor
- Can be disabling

Clinical diagnosis

- Features:
  - Upper extremity high frequency tremor
  - Present with limb movement and sustained posture
  - Head tremor (50%)
  - Voice tremor (30%)
  - Legs or chin (15%)
  - Patients often report tremor improves with alcohol
Essential Tremor

• Criteria 2017
  • Isolated tremor syndrome characterized by bilateral upper-limb action tremor
  • Duration of at least 3 years
  • With or without tremor in other locations (e.g., head, voice, or lower limbs)
  • Absence of other neurologic signs, such as dystonia, ataxia, or parkinsonism

Essential Tremor

• Differential diagnosis:
  – Parkinsonism (no rigidity, bradykinesia, postural instability, or resting tremor)
  – Medication-induced tremor
    • Corticosteroids
    • Valproate
    • Lithium
    • SSRI
    • β-agonist
  – Enhanced physiologic tremor
    • Hyperthyroidism
    • Hyperglycemia
Essential Tremor

- Treatment if tremor interferes with ADLs or causes psychological stress
  - 1st line: propranolol or primidone (tremor reduction 55-60%)
    - Propranolol at dose of 120 to 240 mg per day (SE bradycardia, bronchospasm)
    - Primidone at dose of 250 to 750 mg per day (SE: dizzy, fatigue, malaise, mostly resolves after 1st week)
  - Alternatives (limited data: gabapentin, topiramate, alprazolam, sotalol)
  - Botulinum toxin injection for head tremor when orals ineffective

- 15% have severe disabling tremor
  - Consider deep brain stimulation
    - 60-90% improvement in sx
Summary

• Parkinsonism: think about medication induced before diagnosing PD
• PD is a clinical diagnosis
• Treat with exercise & balance training first (and ongoing)
• Levodopa remains best pharmacologic treatment for motor symptoms
• Can start with DA in younger patients – watch for compulsive behaviors

• Deep brain stimulation reserved for severe motor symptoms on maximal oral medications
• Essential tremor – action & sustained posture
• Rule-out medication induced and enhanced physiologic
• Treat if interfering with function: propranolol or primidone 1st line
MANAGEMENT OF TYPE 2 DIABETES
Which Drugs, For Which Patients?

Robert B. Baron MD MS
Professor and Associate Dean
UCSF School of Medicine
baron@medicine.ucsf.edu

Disclosure
No relevant financial relationships
Management of Type 2 Diabetes

Presentation Outline

- Updates in prevention of complications (other than glycemic control)
- Controversies in glycemic control
- Updates/controversies with diabetes medications

Screening for Diabetes 2019

- BMI ≥25 (or ≥23 in Asian Americans) plus other risk factors
  - Inactivity
  - First degree relative
  - High-risk ethnicity
  - Gestational DM
  - HTN
  - Low HDL or high TG
  - PCOS
  - Acanthosis nigricans
  - Hx CVD
  - Age 45
  - Repeat Q3 years

ADA Diabetes Care, 2019
**Diagnosis of Diabetes 2019**

- A1C ≥ 6.5%
- FPG ≥ 126 mg/dl (7.0 mmol/L)
- 2-h plasma glucose ≥ 200 during OGTT
- Symptoms and random plasma glucose ≥ 200 mg/dl (11.1 mmol/L)
- Need two separate measurements

ADA Diabetes Care, 2019

**Diagnosis of Pre-Diabetes 2019**

- A1C 5.7 – 6.4%
- FPG 100 - 125 mg/dl (5.6mmol/L - 6.9 mmol/L)
- 2-h plasma glucose 140 mg/dl – 199 mg/dl during OGTT (7.8mmol/L – 11.0 mmol/L)

ADA Diabetes Care, 2019
2019 Practice Guidelines: ASA

- Secondary prevention: use in all diabetic patients with ASCVD

- For primary prevention – may be considered use in those at increased CV risk (weak recommendation)

ADA Diabetes Care, 2019

2019 Practice Guidelines: HTN and Tobacco

- BP: Goal < 140 and <90
  - Prefer ACEI or ARB if albuminuria
  - Otherwise ACEI, ARB, CCB, or diuretic
  - With ASCVD may consider <130/<80

- Don’t forget tobacco.
  - Recommend against e-cigarettes
2019 Practice Guidelines: Lipids

- Mostly consistent with ACC/AHA
  - CVD: High intensity statin
  - 40-75: moderate intensity statin
- Differences with ACC/AHA
  - <40 with other risks: consider statin
  - >75: moderate intensity statin
  - If LDL ≥70 on statin, consider second agent

2019 Practice Guidelines: Obesity

- Weight loss of 5% or more
- 16 sessions in 6 months
- Any composition of macronutrients OK (carbs, fat, protein)
- Very low calorie diets (800 kcals per day) may be used
- Weight loss meds may be effective as adjuncts. Weigh benefits and risks
- 150 minutes exercise per week
2019 Practice Guidelines: Bariatric Surgery

- Bariatric (Metabolic) Surgery should be **recommended** for adults with BMI > 35 and type 2 DM, especially if diabetes and comorbidities are difficult to control with lifestyle and meds.

- Bariatric (Metabolic) Surgery should be **considered** for adults with BMI < 35 and type 2 DM, especially if diabetes and comorbidities are difficult to control with lifestyle and meds.

2019 Practice Guidelines: Hospital Care

- Insulin for glucose levels ≥180 mg/dL in most hospitalized patients, with target 140–180 mg/dL.

- Inpatients with adequate nutritional intake: basal + prandial + correction insulin.

- Inpatients with poor nutritional intake or taking nothing by mouth: basal + correction insulin.

- Sliding-scale insulin alone is strongly discouraged.
Case 1

74 year old woman with type 2 diabetes, hypertension, coronary heart disease (s/p MI in 2010), GERD, and osteoarthritis.

Meds: Metformin, glipizide, aspirin, lisinopril, metoprolol, atorvastatin, omeprazole, tylenol, topical diclofenac

Exam: BP 132/80, BMI 29 kg/m²
Normal exam

Case 1

Her glycemic goal should be:

1. HbA1c <6.5%
2. HbA1c <7.0%
3. HbA1c <7.5%
4. HbA1c <8.0%
5. HbA1c <9.0%
**Glycemic Control Update**

- 3 important trials
  - ADVANCE
  - ACCORD
  - VA Diabetes Trial

**ACCORD Trial**

- NIH RCT in DM 2, 10,251 patients, known CVD or risk factors, mean A1c 8.1%

- Intensive vs. standard BP (120 v. 140)
- Lipid control (statins v. statins + fibrates)
- Normalization v. standard BS control (A1c 6 v. 7-7.9)
- Outcomes: CV events. Also microvascular events, quality of life, others
# Management of Type 2 Diabetes

## ACCORD trial

<table>
<thead>
<tr>
<th></th>
<th>Intensive n=5,128</th>
<th>Standard n=5,123</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c achieved:</td>
<td>6.5%</td>
<td>7.5%</td>
<td>-</td>
</tr>
<tr>
<td>1° outcome:</td>
<td>352</td>
<td>371</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>5.0%</td>
<td>3.1%</td>
<td>1.22 (1.01-1.46)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>2.6%</td>
<td>1.8%</td>
<td>1.35 (1.04-1.76)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10.5%</td>
<td>3.5%</td>
<td>-</td>
</tr>
<tr>
<td>Wt. gain&gt;10 kg</td>
<td>27.8%</td>
<td>14.1%</td>
<td>-</td>
</tr>
</tbody>
</table>

**ACCORD Trial**

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>203 11/1000/y</td>
<td>257 14/1000/y</td>
</tr>
</tbody>
</table>

**Number Needed to Harm: 333**

February 2008 (after 3.5 years): NIH stops this arm of study
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>VADT</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

Glycemic Control Summary

- No consistent evidence that tight glycemic control reduces risk of CVD in DM 2
- Possible subgroups with benefit:
  - shorter diabetes duration, no CVD
- Strong evidence of decrease in microvascular disease outcomes with more intensive glucose control
- More hypoglycemia and weight gain with more intensive regimens
Management of Type 2 Diabetes

2019 ADA Practice Guidelines: Glucose Control

- Goal A1C ≤7 for most
- Goal A1C <6.5 for some: short duration, long life expectancy, and no CVD
- Goal less stringent (<8) for history of hypoglycemia, limited life expectancy, advanced micro or macrovascular complications, extensive comorbid conditions, and longstanding DM in whom the goal is difficult to achieve.

Approach to the Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Patient/Disease Features</th>
<th>more stringent</th>
<th>A1C 7%</th>
<th>less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of hypoglycemia/drug adverse effects</td>
<td>low</td>
<td></td>
<td>high</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>newly diagnosed</td>
<td></td>
<td>long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td></td>
<td>short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>Few/mild</td>
<td>severe</td>
</tr>
<tr>
<td>Patient attitude &amp; expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capabilities</td>
<td></td>
<td>less motivated, nonadherent, poor self-care capabilities</td>
</tr>
<tr>
<td>Resources &amp; support system</td>
<td>readily available</td>
<td></td>
<td>limited</td>
</tr>
</tbody>
</table>
Glycemic Control in Older Adults

- For majority of adults older than 65, the harms of HgA1c <7.5 or >9 are likely to outweigh the benefits.

- Optimal targets depend on patient factors, meds, life expectancy, and patient preferences.

- For example: if only need metformin, lower target may be preferred; if need insulin or finger sticks a higher target may be preferred.


2018 ACP Practice Guidelines: Glucose Control

- Personalize goals: benefits and harms, preferences, health status, costs
- A1C between 7% and 8% in most patients
- Deintensify therapy if less than 6.5%
- For patients over 80, or in nursing home, or severe chronic conditions: treat to minimize symptoms and avoid targeting A1C level

ACP Guidelines, Annals Internal Med, 2018
Management of Type 2 Diabetes

2018 AACE/ACE Practice Guidelines: Glucose Control

- A1C ≤6.5 is optimal if it can be achieved in a safe and affordable manner.
- Higher targets (>6.5) may be appropriate for certain individuals (patients with concurrent serious illness and risk of hypoglycemia) and may change over time.

Case 1

Her glycemic goal should be:

1. HbA1c <6.5%
2. HbA1c <7.0%
3. HbA1c <7.5%
4. HbA1c <8.0%
5. HbA1c <9.0%
Case 2: 48 yo woman with DM, BMI 33, on diet and exercise and max dose metformin. HbA1C is now 8.5. Your next best step is:

1. Continue current therapy
2. Begin a sulfonylurea
3. Begin pioglitazone
4. Begin NPH insulin or long-acting insulin analogue
5. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™), saxagliptin (Onglyza™)
6. Begin canagliflozin (Invokana™), dapagliflozin (Farxiga™), empagliflozin (Jardiance™)
Management of Type 2 Diabetes

**Metformin**
- Lowers A1C 1.5-2%
- Weight loss (0-2 kg)
- Lowers triglyceride and LDL; increases HDL
- No hypoglycemia
- No self monitoring
- Inexpensive
- Can be used if GFR >30
- Disadvantages: GI side effects, decreased B12 absorption, (very low) risk of lactic acidosis

**Sulfonylurias**
- Lowers A1C 1.5-2%
- Can be associated with weight gain
- Can cause hypoglycemia
- No self monitoring
- Inexpensive
- Disadvantages: Lack durability in some patients; less CV safety data
Thiazolidinediones (TZD)

- Lowers A1C 0.4-1.5%
- No hypoglycemia when used alone
- Other risks: osteoporosis, bladder cancer with pioglitazone, weight gain edema
- FDA lifted restrictions on rosiglitazone in November 2013
- No hypoglycemia
- No self monitoring
- Strong preference for pioglitazone

Insulin

Introduction of insulin
- Bedtime
- Intermediate/Long-acting insulins
  - NPH, glargine, levemir
  - 10 units
- Self-monitoring of blood glucose (hypoglycemia education)
Management of Type 2 Diabetes

When to go to > 1 shot per day

- HgA1c >7
- Glucose in AM at goal but glucose before dinner >140

Options
- Add premeal lispro/aspart
- Add bid premixed insulin – 70/30, 75/25

Questions
- Continue metformin
- ? Sulfonylurea, ? Thiazolidinedione (mostly not)

Function of Insulin in Regimens

Basal insulin

Meal coverage (carbohydrates)

Correction of high blood sugar
Management of Type 2 Diabetes

INCRETINS

Gut factors that promote insulin secretion in response to nutrients

Major incretins: GLP-1, CCK, GIP

Oral Glucose Promotes More Insulin Release than IV Glucose - Indicating a Role for Incretins
Incretin Drugs

GLP Agonists
- Exenatide (2005/2012)
- Liraglutide (2010)
- Dulaglutide (2014)
- Albiglutide (2014)
- Lixisenatide (2016)
- Taspoglutide
- Semaglutide

DPP IV Inhibitors
- Sitagliptin (2006)
- Saxagliptin (2009)
- Linagliptin (2011)
- Alogliptin (2013)
- Vildagliptin
- Dutagliptin
- Metaglipin
- Gemigliptin
A1C (%) Effect (change from baseline)

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>0.1</td>
<td>-0.4</td>
<td>-0.8</td>
</tr>
<tr>
<td>SFU</td>
<td>0.1</td>
<td>-0.5</td>
<td>-0.9</td>
</tr>
<tr>
<td>MET+SFU</td>
<td>0.2</td>
<td>-0.6</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

Changes in A1C from baseline vs placebo statistically significant.

Weight (change from baseline) & Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Placebo BID</th>
<th>5 mcg exenatide BID</th>
<th>10 mcg exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-1.4</td>
<td>-3.1</td>
<td>-4.2</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>5.3</td>
<td>4.5</td>
<td>5.3</td>
</tr>
<tr>
<td>SFU</td>
<td>3.3</td>
<td>14.4</td>
<td>35.7</td>
</tr>
<tr>
<td>MET + SFU</td>
<td>1.26</td>
<td>19.2</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Open-label extension study to 90 weeks: persistence in weight loss and ↓A1C.
Side Effects

GI
- Nausea (44% vs 18% with placebo); incidence lessens over time; 3% dropout rate due to nausea
- Vomiting (13% vs 4%)
- Diarrhea (13% vs 6%)

Headache (9% vs 6%)
Hypoglycemia (see previous slide)

Improvements in HbA1c With Initial Co-administration of Sitagliptin and Metformin

Mean Baseline HbA1c = 8.8%
N=1091

* Placebo-subtracted LS mean change from baseline at Week 24.
Sit=sitagliptin, Met=metformin.
Aschner P, et al. Oral presentation at the EASD 42nd Annual Meeting; 14-17 September 2006; Copenhagen.
Sitagliptin – Adverse Reactions

<table>
<thead>
<tr>
<th></th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>n = 443</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>23 (5.2)</td>
</tr>
<tr>
<td>+ pioglitazone</td>
<td>n = 175</td>
</tr>
<tr>
<td>Upper resp. infection</td>
<td>11 (6.3)</td>
</tr>
</tbody>
</table>

Small increase in neutrophil count

No nausea or vomiting

No weight loss

Newer Studies of DPP-4 Meds

- Saxagliptin not inferior (nor superior) to placebo for CV outcomes.
  - But statistically significant increase in CHF admissions
  - A1C 0.2% lower

- Sitagliptin not inferior (nor superior) to placebo for CV outcomes.
  - No increase in CHF
  - A1C 0.3% lower

Scirica, NEJM 2013; Green, NEJM 2015
Management of Type 2 Diabetes

CV outcomes with Liraglutide

- RCT, 9340 patients, high CV risk, 3.8 years
  - A1C 0.2% lower

- Fewer events with liraglutide: 13.0% vs. 14.9%

- Fewer deaths with liraglutide: 8.2% vs. 9.6%

Marso SP, NEJM 2016

SGLT-2 inhibitors

- SGLT-2 inhibitors: inhibit sodium glucose cotransporter-2 in proximal tubules where ~90% of glucose filtered through nephron is reabsorbed

SGLT2 Inhibitors
Sodium-glucose cotransporter 2 Inhibitors

- Inhibit glucose reabsorption in renal proximal tubule (*Canagliflozin, Dapagliflozin, Empagliflozin*)

- **Potential advantages**
  - Weight loss (2.5-4kg), low risk of hypoglycemia, reduced BP, lowers A1C about 1%

- **Potential disadvantages**
  - Polyuria, electrolyte disorders, UTI, fungal genital infections, syncope, increased Cr, expensive

---

Empagliflozin, CV Outcomes, and Mortality

- RCT 7020 patients, high risk CV disease, 3.1 years
- Minimal changes in A1C (0.24% lower)
- Reduced combined CV outcome (10.5% vs. 12.1%) and reduced CV (3.7% vs. 5.9%) and all cause mortality (5.7% vs. 8.3%)
  - No difference in stroke or MI
  - No difference when secondary outcomes (unstable angina) included
- Increased genital infections

*N Engl J Med, September 17, 2015*
Canagliflozin Cardiovascular Assessment Study (CANVAS)

- RCT 10,142 patients, Type 2, high risk CV disease, 188 weeks
- Minimal changes in A1C (0.58% lower)
- Modest reduction in combined CV outcome (26.9 vs 31.5 per 1000 patient-years (p=.02)
- No change in all cause mortality
- Less albuminuria and composite renal outcomes
- Higher risk of amputation of toe, feet, leg (6.3 vs 3.4 per 1000 patient years). HR 1.97


Glucose-lowering Medication in Type 2 Diabetes

ADA Dia Care 2019;42:S90-S102

©2019 by American Diabetes Association
Pharmacological Therapy for Type 2 Diabetes

- Metformin is the preferred agent

- In patients with new DM2, marked symptoms, or marked BS or A1C, consider initiating insulin (with or without other agents).

- If monotherapy not at goal and no ASCVD, add second and third oral agent of any class.

ADA Diabetes Care, 2019

Pharmacological Therapy for Type 2 Diabetes

For patients with established ASCVD:

- Metformin is also the preferred agent

- For second med, incorporate agent proven to reduce CV events and mortality: currently empagliflozin and liraglutide

- Canagliflozin may also be considered (reduces CV events)

ADA Diabetes Care, 2018
Pharmacological Therapy for Type 2 Diabetes

- A patient-centered approach should guide selection: efficacy, cost, side effects, weight, comorbidities, hypoglycemia, and patient preference.

- If goal not achieved, consider insulin.

ADA Diabetes Care, 2019

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1C</th>
<th>Cost/month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1-2%</td>
<td>$2</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>1-2%</td>
<td>$4</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.5-1.5%</td>
<td>$5</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>0.5-0.8%</td>
<td>$382</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.5-1.5%</td>
<td>$642</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>0.5-1.5%</td>
<td>$411</td>
</tr>
<tr>
<td>Test strips</td>
<td></td>
<td>$20-$60</td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td>$165</td>
</tr>
<tr>
<td>Glargine 45 U</td>
<td></td>
<td>$298</td>
</tr>
<tr>
<td>YMCA</td>
<td></td>
<td>$67</td>
</tr>
</tbody>
</table>

National Average Drug Acquisition Costs (NADAC)
Management of Type 2 Diabetes

Case 2: 48 yo woman with DM, BMI 33, on diet and exercise and max dose metformin. HbA1C is now 8.5. Your next best step is:

1. Continue current therapy
2. Begin a sulfonylurea
3. Begin pioglitizone
4. Begin NPH insulin or long-acting insulin analogue
5. Begin exenatide (Byetta™), liraglutide (Victoza™), sitagliptin (Januvia™), saxagliptin (Onglyza™)
6. Begin canagliflozin (Invokana™), dapagliflozin (Farxiga™), empagliflozin (Jardiance™)

Conclusions

- Tight control not effective in lowering total or CV mortality (but prevents microvascular complications)
- Many newer agents available: target specific populations, have higher costs, new side effects
- Several agents with hard outcome data, especially for ASCVD risk. High NNT
Conclusions

- Glucose control may be more important early in diabetes
- Good BP, lipid control, smoking cessation is important throughout the course of diabetes
- Prevention of diabetes remains the priority
Common Infections of the Skin

Toby Maurer, MD

Candida of Nails

• Occurs in persons who have hands in water
• Green nails represent the co-pathogen which is pseudomonas

TREATMENT:
• Fluconazole 150 mg qd x1 month PLUS
  Ciprofloxacin 500 bid x 2 weeks
  OR
  Thymol 2-4% soak 20 mins bid x 3 months and
tobramycin or gentamycin ophthalmologic drops
How to diagnose

- Not all dystrophic nails = onychomycosis
- KOH - difficult to do and operator dependent
- CULTURE is gold standard but takes 3 weeks to grow out.
- Now PCR - used in Europe with high sensitivity and specificity
- Cost effective and results in 24-72 hours

Onychomycosis

- Topical treatment – use for the right type of lesions
- Naftin gel for small superficial lesions
- Penlac (Ciclopirox 8%) reported to work 35-52% of the time
  – cost: expensive
Right type of lesions for topicals

- Lunula not affected
- Less than 5 nails affected
- No thickening of nails
- No separation of nail plate on sides

- Griseofulvin-least hepatotoxic but lower efficacy- 250 mg bid x 12-18 months

- Fluconazole- 150 mg qweek for more than 6 months –July 2012 Dermat Tx Gupta AK et al

- Itraconazole- can pulse it- 400 mg qd x 7 days q month x 4 months
Terbinafine (Lamisil)

- Still the leader of the pack—most effective in terms of INITIAL and LONG-TERM cure rate.
- DOSE: 250 mg qd Continuously x 3 months for fingernails and x4 months for toenails (July 2012) i.e. no pulsing
- Seeing terbinafine resistance in India—overuse!!!

<table>
<thead>
<tr>
<th>Medicine</th>
<th>BASELINE</th>
<th>1 YR</th>
<th>5 YR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbinafine</td>
<td>77%</td>
<td>75%</td>
<td>50%</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>70%</td>
<td>50%</td>
<td>13%</td>
</tr>
<tr>
<td>Grispeg</td>
<td>41%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Liver toxicity

- Transaminase elevation 0.4% to 1% with terbinafine and intraconazole
- Transaminase elevation does not predict liver failure
- Liver failure 1/100,000 happens early in course of tx and is unpredictable
- Terbinafine has gone generic
- Warn your pt about development of jaundice, signs of acute hepatitis-stop drug

What about laser?

- Photo- inactivation laser and destructive laser
- 4 studies-2 – no results; 2 show results but with recurrence. Gp treated with laser and topical had fewer recurrences.
Dissecting Cellulitis of Scalp

- Occurs in persons of color
- Culture for tinea but usually bacterial
- Culture and ask lab to provide identification of organism regardless of colony count
- Can take 1-2 years to treat with long-term antibiotics

Tinea Capitis

- Scaling and alopecia
- Examine all children in the family
- “Brush” culture and begin empiric therapy

Treatment
- Gris-PEG: 15-25mg/day x 6 weeks
- Terbinafine 2-4 weeks
  - 62.5mg/kg(10-20kg)
  - 125 mg/day(20-40 kg)
  - 250 mg/day(>40 kg)
Cutaneous Tinea

- KOH is helpful in distinguishing tinea from eczema
- Topical antifungals x 4-6 weeks
- Just say NO to Lotrisone PLEASE!

Pitted Keratolysis

- May be confused with tinea on foot
- See pits
- Bad odor
- From bacteria (corynibacteria)-topical erythromycin bid
**Intertrigo**

- Under pannus and breasts
- Always a component of candida
- Blow dry area
- Topical antifungals
- Tucks pads (wet to dry dressing)

**Tinea Versicolor**

Treatment:
- for localized areas, topical antifungal otherwise:
  - Ketoconazole (Nizoral) 200 mg po daily x 4 days - NOT USING THIS ANYMORE
  - Fluconazole 400 mg x 1; tebinafine 250 qd x 7 days
Recurrent Staph Infection

- Tx for methcillin resistant staph (MRSA) right off the bat-Doxycycline, septra, clinda and cipro
- Eradicate staph for 3 months by adding rifampin 600 qd x 5 days (watch drug-drug interactions) or
- Mupiricin intranasally qd for first 5 days of every month

Recurrent skin infection

- UNDERLYING disease that could be portal of entry
- Dry skin-lubricate with grease
- Eczema/Contact Dermatitis-TAC and lubrication
- Psoriasis-staph exacerbates psoriasis and psoriasis portal of entry
- Tinea- portal of entry-tx with antifungals
If not improving

- Was patient treated long enough?
  Once hair structures are involved or deep tissues, treatment time may be longer

Don’t forget strep

- Strep: Doxycycline and septra may not cover strep
- Cipro/levo do not cover strep
- Add antibiotic that covers strep- Cephalosporins or Dicloxicillin

Jacobs et al Diagn Microb Inf Dis 2007, March
Cellulitis

- Goal in study was to have dermatologists diagnose cellulitis vs other diseases
- 635 pts seen-67% had cellulitis N=425
- 33% had OTHER-eczema, lymphedema, lipodermatosclerosis

*Levell et al Br J of Dermatol (BJD) 2011 Feb*

Lipodermatosclerosis

- Painful
- Reverse champagne bottle appearance of leg
- Responds to pain meds-not antibiotics
- Pain dissipates over a 2 year period
• Of the 425 with cellulitis, 30% had predisposing dermatologic disease like tinea, eczema, psoriasis (treat underlying derm disease!!!)
• Hospitalization was averted for 96% of those with cellulitis (p.o. antibiotics with close follow-up)

Take Home Points:

• Does the patient really have cellulitis?
• Is there an underlying dermatologic cause that contributes to condition-if treated could prevent repeated episodes?
• Does this patient require hospitalization?
Venous Insufficiency Ulcer

• Control Edema
  – Elevation of leg above heart 2 hours twice daily
  – Walk, don’t sit
  – Compression
• Diuretics overused and not of benefit unless fluid retention due to central problem is present (CHF, CRF)
• Create healing wound environment
  *lymphedema /venous ulcers biggest risk factor for recurrent cellulitis (Tay JAAD 2015)

Venous Insufficiency Ulcer

• Metrogel on ulcer-decreases anaerobes
• Semipermeable Dressing (Hydrosorb, Duoderm, etc)
• Compression -
  Unna boot covered by Coban –
  This both provides graded compression AND creates the correct wound environment
• Change dressing weekly
• Refer to dermatology if not healing
When is a Leg Ulcer Infected?

- All leg ulcers are colonized with bacteria. Surface culture of little value
- Suspect infection if:
  - Increasing pain
  - Surrounding erythema, cellulitis
  - Focal area not healing and undermining present
- Treat superficial contaminant with vinegar/Burow’s soaks

Was it an inflammatory condition and not an infection?

- Erythema nodosum
- Pyoderma gangrenosum
- Hidradenitis suppurativa
**Erythema Nodosum**

- Not an infection
- Reaction pattern to strep, cocci, oral contraceptives, estrogen replacement, inflammatory bowel disease, TB and INFLAMMATORY BREAST DISEASE
- Painful, red nodules lower legs
- Pt’s feel bad
- Biopsy diagnosis - inflammation of fat
- Treatment with bedrest, NSAIDS, prednisone

**Pyoderma Gangrenosum**

- Not an infectious disease
- A “reactive” inflammatory disease
- Biopsy diagnosis
- Surgical I&D/excision make it worse
Treatment

- Do Not I&D
- Prednisone/cyclosporine
- Thalidomide
- Tacrolimus (protopic)
- Tx underlying disease

Hidradenitis Supparativa

- Not an infectious disease
- Disease of apocrine glands
- Treatment
  - IL Kenalog
  - Minocycline
  - **NEW**: clindamycin and rifampin for 12 weeks or acitretin

  **NOW** Isotretinoin being used again-best in younger and thinner pts.
  
  - Surgery
  - NOT Antibiotics for bacteria i.e. 10 day course
  - Biologics: infliximab (remicade), adalamumab (humira)
Orolabial Herpes Simplex

- No prophylaxis
- Treat when symptomatic
- Sun exposure can activate HSV-ACV 800 mg 1 hour before sun exposure

- HSV can give an erythema multiforme reaction
- Usually painful targetoid lesions on elbows and knees
Warts

60 different wart types
We have been exposed by the age of 2 to cutaneous warts
60 ways to treat-only 50% efficacy
Tx every 3 wks
LN2 most common
Sal acid effective but use nightly for 3 months at least

Molluscum

• In normal host-self-limited
• LN2 works
• Picking center works
• Retinoids /imiquimod do not work
The Microbiome

- Work being done to better understand the commensal organisms of the skin
- Organisms maintain the integrity of the skin/hair
- *s.* epidermis-important to maintain in order to prevent aberrant inflammatory reactions and cytokine production

Tattoos

- Reactions to dyes
- Koebnerization
- Breaking the skin and introducing infectious disease
Poison Oak Treatment

• Toxin mediated reaction that lasts 3 weeks
• Try to get away with potent topical steroids if localized
• Otherwise prednisone 60 mg po x 10 days then 30 mg po x 10 days and stop
• Alcohol on the trail can serve many purposes!
Somatic Symptom Disorder and Related Disorders:
Clinical Pearls in Assessment and Treatment

Descartes Li, M.D.
Clinical Professor
University of California, San Francisco
descartes.li@ucsf.edu

By Oskar Herrfurth - http://www.goethezeitportal.de/index.php?id=2198,
Public Domain,

Financial Disclosures
none
Case Vignette: Martin

Martin is a 31-year-old married man (Read handout)

1. What is the most likely psychiatric diagnosis? (5min small group discussion)

Somatic Symptom Disorder

A. Somatic Symptoms: One or more somatic symptoms that are distressing and/or result in significant disruption in daily life.

B. One or more of: Excessive thoughts, feelings, and/or behaviors related to these somatic symptoms or associated health concerns:
   1) Disproportionate and persistent thoughts about the seriousness of one’s symptoms (thoughts)
   2) Persistently high level of anxiety about health or symptoms (feelings)
   3) Excessive time and energy devoted to these symptoms or health concern (behaviors)

C. Chronicity: Although any one symptom may not be continuously present, the state of being symptomatic is persistent and lasts > 6 months.

Comments?
Keep in mind

- Get a careful history, including pt’s perspective.
- Prior responses, and consequences.
- Consider the diagnosis in individuals with multiple complaints, such as pain, fatigue, or gastrointestinal problems.
- Individuals often have both a diagnosed medical condition and abnormal behaviors and thoughts related to this condition.
- These individuals are genuinely suffering.

Behavior Perspective

Behavior 

Choice 

Consequences

Rumination → increased likelihood
Consequent beh → worsened symptoms
Examples of Disease Entities That Overlap with Somatic Symptom and Related Disorders

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Disease Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>Chronic fatigue syndrome</td>
</tr>
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<td>ENT</td>
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</tr>
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<td>Psychogenic non-epileptic seizures</td>
</tr>
<tr>
<td></td>
<td>(Conversion disorder)</td>
</tr>
</tbody>
</table>

Case Vignette:: Martin

2. Patients may have strong reactions to having this kind of disorder. What are they and how can physicians help them with these reactions?

*How do you think Martin might feel about the situation?*
Challenges

Hint: How do you think someone would feel if they were in Martin’s situation? How might Martin feel once he is told that he has this disorder?

- invalidated
- abandoned and worried about being referred elsewhere.
- uncertainty and lack of trust
- very alone and confused

Tips on how to manage SSD

Avoid direct confrontation about the truthfulness of the symptoms

Reassure pts that:

- You understand that the symptoms are distressing
- you won’t abandon them – pts may feel very isolated and often have chronic illnesses that must be managed
- You understand how confusing it is to have symptoms and yet not know if they are portend a serious illness or if they are just normal bodily symptoms
Tips on how to manage SSD

Normal lab tests:
- Are reassurance that nothing catastrophic is going on,
- Are useful because they have “ruled out” many of the important diseases
- Do NOT mean that what the patient is experiencing isn’t happening.

• Help the person identify creative and practical solutions and coping strategies
• Remember that since they may feel alone and isolated, support groups, exercise/physical therapy, or psychotherapy can be helpful

Case Vignette:: Martin

3. What is it like to be in the role of Dr. Smith?
Any tips to share about how to manage countertransference?

How do you think Dr. Smith might feel about the situation? How might Dr. Smith feel about approaching Martin with the diagnosis and treatment plan?
Tips on how to manage countertransference

Learn more about the disorder
Other physician wellness techniques

Case Vignette: Martin

4. Discuss each of the following clinical principles/interventions and their applicability in this patient:

How do you think Dr. Smith might feel about the situation? How might Dr. Smith feel about approaching Martin with the diagnosis and treatment plan?
<table>
<thead>
<tr>
<th>Principle/intervention</th>
<th>Comment (yes/no, then discussion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The focus should be complete remission of symptoms.</td>
<td>No, care rather than cure</td>
</tr>
<tr>
<td>Discuss social issues that may be distressing with patient.</td>
<td></td>
</tr>
<tr>
<td>Have a high threshold for ordering tests</td>
<td>Yes, attempt to have diagnostic and therapeutic conservatism. Review old records, “laying on of hands” Be especially conservative with ordering high-risk, low-yield evaluations.</td>
</tr>
<tr>
<td>Instruct patient to return to clinic for follow-up “as needed”.</td>
<td></td>
</tr>
<tr>
<td>Instruct patient to go to Emergency Department “as needed”</td>
<td>No, symptoms production and perpetuation</td>
</tr>
<tr>
<td>Liberally use benign remedies</td>
<td>Yes, recommendation and use of benign remedies may help the patient to feel supported. Consider routine use of physical/occupational/recreational therapy</td>
</tr>
<tr>
<td>Refer to psychiatrist as soon as possible.</td>
<td></td>
</tr>
<tr>
<td>Special attention to stable and consistent healthcare relationships</td>
<td></td>
</tr>
<tr>
<td>Family engagement</td>
<td></td>
</tr>
</tbody>
</table>
Thus far

- Martin: Somatic Symptom Disorder

Case Vignette: Robin

1. What is the most likely psychiatric diagnosis?  
   *(Read handout)*
DSM-5 Criteria for Illness Anxiety Disorder

A. **Preoccupation** with having or acquiring a serious illness.
B. Somatic symptoms are **not present or are only mild**
C. **High level of anxiety** about health, and easily alarmed about personal health status.
D. **Excessive health-related behaviors or maladaptive avoidance**
E. **at least 6 months**
F. Not better explained by another disorder.

Former diagnosis: hypochondriasis

Superseded by:
- somatic symptom disorder (75%)
- illness anxiety disorder (25%)
What is the difference between somatic symptom disorder and illness anxiety disorder?

- Both may present with anxiety
- Illness anxiety disorder with no symptoms (or only mild), and fears developing an illness
- Somatic symptom disorder often has a medical condition with symptoms, but the reaction to these symptoms is maladaptive
Keep in mind

- Get a careful history, including pt’s perspective.
- Prior responses, and consequences.
- Consider the diagnosis in individuals with multiple complaints, such as pain, fatigue, or gastrointestinal problems.
- Individuals often have both a diagnosed medical condition and abnormal behaviors and thoughts related to this condition.
- These individuals are genuinely suffering.

[Examples of Disease Entities That Overlap with Somatic Symptom and Related Disorders]

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Can be conceptualized as “contested illnesses”
Case Vignette: Robin

2. How is Robin’s clinical presentation different from Martin’s?

3. What other psychiatric disorders should we consider Robin’s case?

Key rule outs for somatic symptom disorder and related disorders

1. Psychosis
2. Anxiety disorders, especially OCD
3. Cultural syndromes
4. Factitious disorders*

Each has a different management approach.
*separate section on factitious disorders
1. Psychosis
- Work with psychiatrist to manage delusions
- If psychosis with poor insight, recommend: I Am Not Sick, I Don’t Need Help: How To Help Someone With Mental Illness Accept Treatment, by Xavier Amador
- Consider diagnoses besides schizophrenia

2. Obsessive Compulsive Disorder
- If OCD is diagnosed, treat using SSRIs/clomipramine and Exposure-response prevention

For OCD with disease obsession, what would the exposure and response prevention look like?
3. Cultural syndromes

- May overlap with “contested illnesses” (e.g., Morgellon’s)
- Need to understand specifics of each syndrome
What is a “cultural syndrome”?

- Occur only in certain cultures (or subcultures)
- Arise out of prevailing cultural beliefs
- Recognized by individuals in the culture

Asian Cultural Syndromes

Shuo-yang or Koro (Chinese)
Shen-Kui (Chinese)
Shen-jing shuai-ruo -- neurasthenia
Hwa-byung (Korean)
Taijin kyofusho (Japanese)
Hikikomori (Japanese)
Fan death (Korean)
Cultural syndromes are best understood from an emergent perspective.

That is, when cultural beliefs interact with individuals to generate illness.
Thus far

- Martin: Somatic Symptom Disorder
- Robin: Illness Anxiety Disorder

Management of Chronic Major Somatization

1) Care Rather Than Cure
   Don’t try to eliminate symptoms completely
   Focus on coping and functioning as goals of treatment

2) Diagnostic and Therapeutic Conservatism
   Review old records before ordering tests
   Respond to requests carefully
   *(remember these pts often have medical conditions)*
   Benign remedies

(Adapted from Barsky AJ. Clinical Crossroads: A 37-Year-Old Man With Multiple Somatic Complaints. *JAMA* 1997; 278: 673-9)
Management of Chronic Major Somatization

3) Validation of Distress
Don’t refute or negate symptoms
Patient-physician relationship not predicated on symptoms
Focus on social history
Regular visits (not prn)
  – consider scheduled telephone contacts

(Adapted from Barsky AJ. Clinical Crossroads: A 37-Year-Old Man With Multiple Somatic Complaints. JAMA 1997; 278: 673-9)

Management of Chronic Major Somatization

4) Providing a Diagnosis
Emphasize dysfunction rather than pathology
Describe amplification process
  provide specific example, if appropriate
Cautious reassurance, dispel:
  “Every symptom must have an explanation”
Introduce stress model of disease, if appropriate

5) Mental Health Consultation
To diagnose psychiatric comorbidity
For recommendations about pharmacotherapy
For cognitive-behavioral therapy to improve coping or psychotherapy

(Adapted from Barsky AJ. Clinical Crossroads: A 37-Year-Old Man With Multiple Somatic Complaints. JAMA 1997; 278: 673-9)
Also

Referral to cognitive-behavioral therapy either individually or groups may be helpful.
Groups may be more cost-effective and provide social support to the patient.

Case Vignette: Karen

24-year-old medical student with a history of knee osteosarcoma and chemotherapy passed out while on rounds one morning.

Labs revealed: Hemoglobin of 5.2g/dL, MCV112. She was admitted to the hospital.

Soon thereafter, her parents flew in from out of town and found numerous bottles of the patient’s blood in her apartment.
Case Vignette: Karen

24-year-old medical student

1. What is the most likely psychiatric diagnosis? (support your answer)

2. How does Karen’s disorder differ from Martin’s or Robin’s?

3. What are your basic principles/clinical pearls in managing this disorder?

Factitious Disorder

*Imposed on Self*

A. Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception.

B. Presents self to others as ill, impaired, or injured.

C. **Evident even in the absence of obvious external rewards.**

D. Not better explained by another mental disorder

Specify: Single episode or Recurrent episodes
Factitious disorder*

*assessment tips*

- Trace development of symptoms over time
  - Symptoms often emerge or change over time (shaping)
- Look for modeling, rewards, explicit instructions, medical backgrounds
- Patients are often immature or dependent, with limited problem solving skills.
- He or she may be easily suggestible and hypnotizable [http://hypnosis.tools/suggestibility-scales.html](http://hypnosis.tools/suggestibility-scales.html)

*These tips also apply to conversion disorder*

---

Munchausen’s syndrome

non-DSM term for a severe form of factitious disorder

- Characterized by recurrent hospitalization, travelling, and dramatic, untrue, and extremely improbable tales of their past experiences
Factitious disorder
*assessment tips*

Management principles to follow

---

Thus far

- Martin: Somatic Symptom Disorder
- Robin: Illness Anxiety Disorder
- Karen: Factitious Disorder
Case Vignette

16yo girl with new onset tics

What Happened to the Girls in Le Roy?

https://youtu.be/cCED0PQqXZg

What Happened to the Girls in Le Roy?


Case Vignette

16yo girl with new onset tics

What is your diagnosis?
DSM-5 Criteria for Conversion Disorder
(Functional Neurological Symptom Disorder)

A. **One or more symptoms of altered voluntary motor or sensory function.**
B. **Incompatibility between the symptom and recognized neurological or medical conditions.**
C. Is not better explained by another medical or mental disorder.
D. Causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

Specify symptom type: abnormal movement, seizures, speech, sensory loss, etc.
Specify if: acute or persistent
Specify if: with or without psychological stressor (specify stressor)

History of conversion disorder

**DSM-II: Hysterical neurosis**

Hystoria → psychosomatic → somatoform

<table>
<thead>
<tr>
<th><strong>History of the DSM</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-I (1952)</td>
</tr>
<tr>
<td>DSM-II (1968)</td>
</tr>
<tr>
<td><strong>DSM-III (1980)</strong></td>
</tr>
<tr>
<td>DSM-IV (1994)</td>
</tr>
<tr>
<td>DSM-5 (2013)</td>
</tr>
</tbody>
</table>

the DSM-II, hysterical neurosis
Hystero-epilepsy

Other examples of conversion disorder

- psychogenic non-epileptic seizures (PNES) aka pseudoseizures
- Sudden paralysis of right upper extremity
- Sudden onset of unilateral hearing loss
- Also hysterical blindness, incontinence
Case Vignette

16yo girl with new onset tics,
Suppose she had a history of epilepsy
Could this be psychogenic non-epileptic seizures?

Characteristics of PNES

1. triggered by stress
2. no incontinence
3. no post-ictal confusion
4. speaking during the episode
5. >10minutes
6. always witnessed
7. resolution with psychosocial interventions
Risk factors

How do you treat Conversion disorder?
How to Treat Conversion Disorder

Conversion disorder is a functional neurological symptom condition in which a person experiences physical sensations such as pain or loss of feeling due to psychological stress. A person with conversion disorder endures a stressful or frightening event and then converts this psychic crisis that accompanies the event into a physical complaint. If someone you know has conversion disorder, the person will probably be very confused when their doctor explains that there seems to be no underlying physical cause to symptoms. Learn how to overcome this condition through various treatment approaches and by managing stress.

Method 1: Identifying Conversion Disorder

- **Signs and Symptoms**
  - Physical symptoms that are not caused by a physical disorder or injury.
  - Symptoms that improve or worsen based on emotional or psychological factors.
  - Symptoms that are not consistent with the medical examination.

- **Causes**
  - Psychological factors such as stress, anxiety, or trauma.
  - Psychological disorders such as depression or anxiety.
  - Other medical conditions.

- **Symptoms**
  - Physical symptoms that are not caused by a physical disorder or injury.
  - Symptoms that improve or worsen based on emotional or psychological factors.
  - Symptoms that are not consistent with the medical examination.

- **Treatment**
  - Psychological therapy such as cognitive-behavioral therapy (CBT).
  - Medication for underlying mental health conditions.
  - Support from friends, family, and healthcare professionals.

- **Prevention**
  - Managing stress and anxiety.
  - Developing coping strategies for stress.
  - Regular physical activity.
  - Good sleep habits.

http://www.neurosymptoms.org/
Conversion disorder management

https://vimeo.com/136982979

The Fringe 2015: Hidden World of Functional Disorders

conversion disorder management

- Can be very useful to be straightforward and educational
- Attitude and word choice may be key
- Reassure that condition usually resolves with treatment (PT, stress reduction)
- However, conversion may overlap with management of factitious disorder
Summary

• Martin: Somatic Symptom Disorder
• Robin: Illness Anxiety Disorder
• Karen: Factitious Disorder
• Theresa: Conversion

Is this factitious disorder?
What about the 16 other girls? Malingering? Cultural syndrome? Mass hysteria?

Factitious disorder management

Remember:
- The patient’s need to be consistent can be the crucial sustaining factor
- Confrontation is often dramatically unsuccessful
- Successful outcome often depends upon persuasion and countersuggestion
Factitious disorder management

- Sometimes ignoring the symptoms is sufficient
- Communicate expectation of resolution
- Suggest a disease course
- Offer improvement without embarrassment

- Graduated prescriptions: e.g., physical therapy
- Let go of the need to be right
- For more complex cases, a team/systems approach is critical (high level expertise required)

Summary

- Martin: Somatic Symptom Disorder
- Robin: Illness Anxiety Disorder
- Karen: Factitious Disorder
- Theresa: Conversion
  *(vs. Factitious disorder)*
Factitious Disorder
*Imposed on others*

also known as Munchausen syndrome by proxy

There is growing consensus in the pediatric community that this disorder should be renamed "medical abuse" to highlight the harm caused by the deception and to make it less likely that a perpetrator can use a psychiatric defense when harm is done.

http://www.msnbc.com/msnbc/disturbing-testimony-mommy-blogger-lacey-spears-trial

---

Factitious Disorder
*Imposed on others*

**Does it only occur with women?**

- No, it appears that whomever is the primary caregiver can be.
- Prior history of factitious disorder appears to be a common risk factor.
- Male perpetrators more likely to incur criminal prosecution with more punitive sentences.

Take Home Points

• Medical conditions and somatic symptom and related disorders often co-occur (eg, epilepsy and seizures of non-epileptic origin)
• It may be impossible to prove the diagnosis definitively.
• Countertransference may be intense, and may be a clue to the diagnosis
• A consultation from outside the team can be essential.

Is this malingering?
Malingering

• creation of physical signs or symptoms to gain attention or avoid something adverse.
• “know what they are doing and why they are doing it”
• the benign use of feigned illness

Summary

• Martin: Somatic Symptom Disorder
• Robin: Illness Anxiety Disorder
• Karen: Factitious Disorder
• Theresa: Conversion

(vs. Factitious disorder
Vs. Malingering)
Is this mass hysteria? A cultural syndrome or a “contested illness”? 

https://www.newyorker.com/magazine/2017/04/03/the-trauma-of-facing-deportation
Resignation Syndrome: Catatonia? Culture-Bound?

Not Catatonia!


What is a “contested illness”?

(1) Sufferers denied healthcare and legitimacy
(2) Institutions justify denial of care
(3) Patients respond collectively

→The result is the maintenance of these very expensive struggles for all involved

Examples of contested illnesses

- Chronic fatigue syndrome
- Multiple chemical sensitivity
- ADHD
- Fibromyalgia
- Pre-menstrual dysphoric disorder
- Gulf War-related illnesses
- Morgellon’s syndrome
- Resignation syndrome

## Symptom Expression

<table>
<thead>
<tr>
<th>Unconscious Motivations</th>
<th>Voluntary</th>
<th>Involuntary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Somatic Symptom Disorder</td>
<td>Factitious Disorders</td>
</tr>
<tr>
<td></td>
<td>Illness Anxiety Disorder</td>
<td>Imposed on self</td>
</tr>
<tr>
<td></td>
<td>Conversion d/o (functional neurological symptom disorder)</td>
<td>Imposed on Another</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Malingering</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benign use of feigned illness</td>
</tr>
</tbody>
</table>

Psychological factors affecting other medical conditions

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## Summary

- **Martin:** Somatic Symptom Disorder
- **Robin:** Illness Anxiety Disorder
- **Karen:** Factitious Disorder
- **Theresa:** Conversion
  
**Vs. Factitious disorder
Vs. Malingering
Vs. cultural syndrome/contested illness**
Effective Weight Management

OBESITY AND WEIGHT MANAGEMENT IN OFFICE PRACTICE

Robert B. Baron MD MS
Professor of Medicine
Associate Dean for GME and CME
Director, UCSF Weight Management Program

Declaration of full disclosure: No conflict of interest

Effective Weight Management

- Measure BMI and document obesity
- Assess obesity-related risks
Effective Weight Management

- Talk about weight
  - “Your weight is above a healthy range.”
  - “Changes in weight may help you manage your X.”

Effective Weight Management

- Assess eating habits and activity.
- Ask about goals.
- What changes willing to start?
- Willing to work with me and my team?
Effective Weight Management

- Discuss your goals.
- Discuss difference between weight loss and weight maintenance.

Effective Weight Management

- Make specific recommendations about
  - exercise
  - diets
  - medications
  - surgery
SUMMARY

- Environmental and public health changes work.
- Diets work, but not for long in most people (but they do for some).
- Exercise improves health independent of weight change and aids in weight maintenance.

SUMMARY

- Meal replacement products promote greater weight loss (but mostly in the short term).
- Medications achieve small amounts weight loss for as long as agents can be used (but little is known about long term outcomes).
- Surgery results in long term weight loss and reductions of diabetes and mortality (but with complications in some, weight regain, and a high number needed to treat).
OVERALL GOALS OF MANAGEMENT

- Be as fit as you can be at your current weight
- Don’t gain any more weight
- If highly motivated, attempt weight loss

Michael Pollan’s Three Rules

- Eat food
- Not too much
- Mostly plants
Baron’s Additional Rules

- Eat unprocessed foods
- Eat the right amount to maintain your weight
- Eat something colorful at every meal (and every snack)
- Don’t drink calories
- If can’t make the “best” choice, make a better choice
- Be as fit as you can be: exercise daily
- Eat with your children; eat at home

The “Generic” Diet

- Continued debate: macronutrient balance, amounts of meat/fish/fowl, other specific foods

- But almost all agree: limit sugar, refined grains, large amounts of saturated and trans fat. Eat fruits and vegetables, healthy oils, whole grains, legumes and nuts

- Bottom line: master a “generic” diet for patients and self

Baron, RB JAMA Int Med, 2013
Effective Weight Management

More Information

Dietary Guidelines for Americans
http://health.gov/dietaryguidelines

CDC Division of Nutrition, Physical Activity & Obesity
www.cdc.gov/nccdphp/dnpao/index.htm

USDA Nutrition.gov: http://www.nutrition.gov/

Center for Science in the Public Interest (CSPI):
http://www.cspinet.org/

ChooseMyPlate: http://www.choosemyplate.gov/

More Information

FDA: Food Labeling and Nutrition
https://www.fda.gov/food/food-labeling-nutrition

Nutrition.gov: Shopping, Cooking & Meal Planning:
http://www.nutrition.gov/shopping-cooking-meal-planning

Healthy Eating Plate (Harvard):
http://www.hsph.harvard.edu/nutritionsource/what-should-you-eat-pyramid/
I have no disclosures relevant to this talk

General Disclosures

- Bayer: litigation consultant
- Sebela Pharmaceuticals:
  - Investigator proctor in phase III trial of a copper IUD (VeraCept)
## US Medical Eligibility Criteria

<table>
<thead>
<tr>
<th>Cat</th>
<th>Definition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No restriction in use</td>
<td>Use the method</td>
</tr>
<tr>
<td>2</td>
<td>Advantages generally outweigh theoretical or</td>
<td>More than usual follow-up needed</td>
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<tr>
<td></td>
<td>proven risks</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Theoretical or proven risks outweigh advantages</td>
<td>Clinical judgment that the patient can use safely</td>
</tr>
<tr>
<td>4</td>
<td>Unacceptable health risk if the method is used</td>
<td>Do not use the method</td>
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</tbody>
</table>
• U.S. Selected Practice Recommendations for Contraceptive Use, 2016. *MMWR* July 29, 2016. 65(4);1–66

**2016 Updates to the US MEC and SPR**

• New recommendations for women with
  – Cystic fibrosis
  – Multiple sclerosis
• Interactions with SSRIs and St. John’s wort
• Addition of ulipristal acetate to ECP section
• Major revisions for hormonal methods
  – Women with migraine headaches
  – Women using antiretroviral therapy
  – Breastfeeding & progestin-only contraception
My opinion: use by clinicians should be a quality metric!!

Filling The “Gaps”

- Pregnancy testing and counseling
- Achieving pregnancy
- Basic infertility
- Preconception health
- Preventive health screening of women and men
- Contraceptive counseling, incl reproductive life plan
Lilly

- 33 year old G₃P₃ established patient seen for family planning health screening visit
- Using metformin for type 2 diabetes
- Mutually monogamous relationship
- Recent fasting lipid profile normal
- LMP 3 weeks ago; using condoms for contraception
- Cervical cytology test 2 years ago was negative
- Screened negative for HIV in each of her 3 pregnancies
Lilly

- Would like to start oral contraceptives...today if possible
  - 13 cycles of monophasic dispensed
- **What needs to be done in regard to...**
  - Counseling ?
  - Method choice?
  - Physical assessment?
  - Screening tests?

Diabetes and Contraception

- Progestins may increase insulin resistance, but not to the point of clinically significant ▲ blood glucose
- Estrogen increases risk of thrombosis in vessels damaged by diabetic vascular disease
- CHC may be used in diabetics in the *absence* of clinically-manifest vascular disease, including
  - Retinopathy, nephropathy
  - Peripheral vascular disease, heart disease
**US MEC 2016: Diabetes**

<table>
<thead>
<tr>
<th></th>
<th>OC/P/R</th>
<th>POP</th>
<th>DMPA</th>
<th>Impl</th>
<th>LNG-IUD</th>
<th>Cu-IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx gestational diabetes</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nonvascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i. Noninsulin-dependent</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ii. Insulin-dependent</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nephropathy/retinopathy/</td>
<td>3/4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other vascular disease or</td>
<td>3/4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>diabetes of &gt;20 yrs’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**SPR Appendix B: When To Start Using Specific Contraceptive Methods**

<table>
<thead>
<tr>
<th>Method</th>
<th>When to start</th>
<th>Back-Up</th>
<th>Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu-IUC</td>
<td>Anytime</td>
<td>none</td>
<td>pelvic exam</td>
</tr>
<tr>
<td>LNG-IUS</td>
<td>Anytime</td>
<td>If &gt;7d*</td>
<td>Pelvic exam</td>
</tr>
<tr>
<td>Implant</td>
<td>Anytime</td>
<td>If &gt;5d*</td>
<td>none</td>
</tr>
<tr>
<td>Injection</td>
<td>Anytime</td>
<td>If &gt;7d*</td>
<td>none</td>
</tr>
<tr>
<td>CHC</td>
<td>Anytime</td>
<td>If &gt;5d*</td>
<td>BP</td>
</tr>
<tr>
<td>POP</td>
<td>Anytime</td>
<td>If &gt;5d*</td>
<td>none</td>
</tr>
</tbody>
</table>

* After the first day of menstrual bleeding
SPR Appendix C: Exams And Tests Needed Before Method Initiation

<table>
<thead>
<tr>
<th>Examination</th>
<th>Needed for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>OC, patch, ring</td>
</tr>
<tr>
<td>Clinical breast examination</td>
<td>None</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>Hormonal methods</td>
</tr>
<tr>
<td>Bimanual examination, cervical inspection</td>
<td>IUC, cap, diaphragm</td>
</tr>
<tr>
<td>Glucose, Lipids</td>
<td>None</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>None</td>
</tr>
<tr>
<td>Thrombogenic mutations</td>
<td>None</td>
</tr>
<tr>
<td>Cervical cytology (Papanicolaou smear)</td>
<td>None</td>
</tr>
<tr>
<td>STD screening with laboratory tests</td>
<td>None</td>
</tr>
<tr>
<td>HIV screening with laboratory tests</td>
<td>None</td>
</tr>
</tbody>
</table>

Diabetes and Contraception: Management

- Combined hormonal contraceptives
  - Evaluate CV risk profile
  - Use low E (thrombosis) + low P (glucose control)
  - Adjust insulin or oral hypoglycemic as necessary
- Progestin only methods
  - May cause insulin resistance and ▲ blood glucose, but usually clinically insignificant
  - Do not increase risk of arterial thrombosis
- IUDs are safe and effective choice
Lilly: Management

• QFP: counseling based upon shared decision making
• MEC: can use OCs with same day start
• SPR: assess BP, BMI only
• STD: no STI screening tests indicated
• HIV: screening not necessary
• Cervical cancer screening: up to date
• Breast cancer screening: clinical breast exam optional
• Pre-pregnancy care
  – *Discuss pre-pregnancy glucose control with diabetics*

ADA 2015 Guidelines: Preconception Care

<table>
<thead>
<tr>
<th>Maintain A1c levels as close to 7.0% as possible before conception</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women of childbearing potential</td>
</tr>
</tbody>
</table>
| Evaluate and treat women contemplating pregnancy | • Retinopathy  
• Nephropathy  
• Neuropathy  
• CVD |
| Evaluate and consider risk/benefit profile of medications used for DM | Contraindicated/not recommended  
• Statins  
• ACEIs (AT-converting enzyme inhibitor)  
• ARBs (AT receptor blocker)  
• Non-insulin therapy, except metformin |

ADA, Diabetes Care 2015; 38 (supp 1): 77-79
Hillary

• 19 year old G0 woman is seen for a periodic health screening visit (aka, a “Well Woman” visit)
• Same male partner for the past year
• Feeling well; no complaint of vaginal discharge, abnormal bleeding, dyspareunia
• Weight: 210 pounds; BMI: 32 kg/m²
• Using contraceptive patch; asks about insertion of LNG-IUS
• Questions…
  – Which methods are acceptable relative to BMI and age?
  – What needs to be done at her “check-up” visit?

Body Weight and Contraception

• Four issues about body weight relate to each method
  – Will the method cause excess weight gain?
  – Is the failure rate higher in obese women?
  – Are there medical risks attributable to the method in obese women (compared average weight)?
  – What is the WHO-MEC category and why?
• Pregnancy and childbirth among obese women are far more dangerous than are either contraception or sterilization
### Body Weight and Contraception

<table>
<thead>
<tr>
<th></th>
<th>OC</th>
<th>Patch</th>
<th>DMPA</th>
<th>Implant</th>
<th>IUC</th>
<th>Tubal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>↑ failure rate in obese</td>
<td>No</td>
<td>No</td>
<td>Yes#</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Medical risk in obese women</td>
<td>↑DVT risk</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>Difficult insertion</td>
<td>Surgical complications</td>
</tr>
<tr>
<td>US-MEC</td>
<td>2</td>
<td>2</td>
<td>1/2 **</td>
<td>1</td>
<td>1</td>
<td>Not rated</td>
</tr>
</tbody>
</table>

* Mainly in obese adolescents and those who experience a >5% body weight increase within 6 months of DMPA initiation
# If weight > 90 kg, increase of 2-4 failures/100 couples/year
** < 18 yrs of age and ≥30 kg/m² BMI

### US MEC: Age and Parity

<table>
<thead>
<tr>
<th>OC/ P/R</th>
<th>POP</th>
<th>DMPA</th>
<th>Implant</th>
<th>LNG-IUS</th>
<th>Cu-IUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 yo: 1</td>
<td>&lt;40 yo: 1</td>
<td>&lt;18 yo</td>
<td>&lt;18 yo</td>
<td>&lt;20 yo: 2</td>
<td>&lt;20 yo: 2</td>
</tr>
<tr>
<td>&gt;40 yo: 2</td>
<td>&gt;40 yo: 1</td>
<td>18-45 yo: 1</td>
<td>18-45 yo: 1</td>
<td>&gt;20 yo: 1</td>
<td>&gt;20 yo: 1</td>
</tr>
<tr>
<td>&gt;45 yo: 2</td>
<td>&gt;45 yo: 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Nullip | 1 | 1 | 1 | 1 | 2 |
| Parous | 1 | 1 | 1 | 1 | 1 |
SPR: Initiation of LNG-IUDs

Timing

• The LNG-IUD can be inserted at any time if it is reasonably certain that the woman is not pregnant

Need for Back-Up Contraception

• If inserted ≤7 days since LMP, no additional protection
• If inserted >7 days since LMP, abstain from intercourse or use additional protection for the next 7 days

Examinations and Tests Needed Before Initiation of a Cu-IUD or an LNG-IUD

• Bimanual exam and cervical inspection are necessary
• Screen for CT and GC according to national guidelines
  – If not yet screened, perform at the time of insertion
• If purulent cervicitis or GC or CT, do not place IUD (MEC-4)
• If a very high individual likelihood of STD exposure generally should not have IUD insertion (MEC-3)
**SPR: IUD Recommendations**

- Prophylactic antibiotics not recommended
- Pre-treatment with misoprostol not recommended
- Routine follow-up after IUD insertion
  - No routine follow-up visit is required
  - Advise a woman to return at any time
    - To discuss side effects or other problems
    - If she wants to change the method
    - When it is time to remove or replace the IUC

**Obese Adolescent and Contraception: Management**

- DMPA is not an ideal choice for her because of the potential for additional weight gain
  - If DMPA chosen, baseline weight and recheck in 6 months
- All methods work as well in obese women as with average weight women, except the contraceptive patch
- The efficacy of emergency contraceptive pills is poor in obese women
- IUCs and implants are an excellent choice for adolescents, obese women, and obese adolescents
Priscilla

- Is a married 22 year old G₂ P₀ TAB₂ established client who is seen for pregnancy determination visit
- Her first two pregnancies were at 17 and 19 years old and occurred while using condoms
- She stated that she has occasional “sick headaches”
  - No aura before headaches begin
  - Most headaches occur during menstrual period
- She does not want to become pregnant now
- Interested in starting OCs
- Visit 38 minutes; 25 minutes counseling

Migraine Headache: Complications

- Migraine with aura associated with stroke risk
  - An increased relative risk
  - A low absolute risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds ratio</th>
<th>Stroke/10,000/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>No migraine or OCs</td>
<td>1.0</td>
<td>6</td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>2-4</td>
<td>18</td>
</tr>
<tr>
<td>Migraine + COCs</td>
<td>6-14</td>
<td>54</td>
</tr>
<tr>
<td>Migraine with smoking</td>
<td>7-10</td>
<td></td>
</tr>
<tr>
<td>Migraine + smoking + OC</td>
<td>34.4</td>
<td></td>
</tr>
</tbody>
</table>

Edlow AG, Bartz D. Rev in Obstet Gynecol, 2010; 3(2): 55-65
### US MEC 2010: Headaches

<table>
<thead>
<tr>
<th></th>
<th>OC/P/R</th>
<th>POP</th>
<th>DMPA</th>
<th>Impl</th>
<th>LNG-IUD</th>
<th>Cu-IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-migrainous</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Migraine</td>
<td>I</td>
<td>C</td>
<td>I</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without aura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≤ 35</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt; 35</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>With aura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Any age</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

I: Initiate
C: Continue

### US MEC 2016: Headaches

<table>
<thead>
<tr>
<th></th>
<th>OC/P/R</th>
<th>POP</th>
<th>DMPA</th>
<th>Impl</th>
<th>LNG-IUD</th>
<th>Cu-IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-migrainous</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Migraine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without aura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2*</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>With aura</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Classification is for women without any other risk factors for stroke (e.g., age, hypertension, and smoking)
Headaches and Contraception
Management

- Differentiate migraine from non-migraine headaches
  - If unclear, seek neurologist consultation
- Menstrual headaches: extended regimen OCs or NuvaRing
- CHC in women with migraines without aura
  - Use low estrogen dose product
  - Recommend frequent follow-up visits initially
  - If HA worsening frequency or severity, or new neurological symptoms, discontinue CHC
- Progestin-only methods, IUC are safe and effective

Jena

- 19 years old
- Born at 26 weeks; birth weight 1100 grams
- Both visual and hearing difficulties since childhood
- Now has mood problems
- Complains of irregular, heavy menses + dysmenorrhea...would like her periods to stop!
- Sexually active with 19 year old male
- PE: BMI =34 kg/m², BP = 118/72; mild facial hirsutism
- Challenge: contraception + optimize bleeding suppression
PCP/ Women's Health Visit
Ask re: menstrual pattern/hygiene, sexual activity

+ Menstrual problems
  Sexually active*?
  Yes
  - LNG-IUS
  - DMPA
  - Extended OCs
  - POP
  - NSAIDs
  - LNG-IUS
  - DMPA
  - Extended OCs

Extremely rarely
  - EM ablation
  - Hysterectomy

No menstrual problems

Yes
  - Copper IUD
  - LNG-IUS
  - Implant
  - DMPA
  - Extended OCs
  - POP
  - Patch

No
**Menstrual Manipulation for Adolescents with Physical and Developmental Disabilities**

- Optimal suppression...reduction in amount and days of flow
- NSAIDs decrease ovulatory menstrual bleeding by 30–40%
  - Naproxen sodium 220-440 mg BID
  - Ibuprofen 400-600 mg TID
- Combined OCs for an extended period or continuous use


---

**Menstrual Manipulation for Adolescents with Physical and Developmental Disabilities**

- POPs can be used, but efficacy is dependent on adherence to use at the same time each day
- DMPA results in high rates of amenorrhea by 4th dose
- LNG IUD should be considered
  - Irregular bleeding is common initially, but amenorrhea over time and blood loss is decreased

## Contraception + Less Bleeding

<table>
<thead>
<tr>
<th>Method</th>
<th>Tier</th>
<th>Efficacy</th>
<th>Advantages</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNG-IUS</td>
<td>1</td>
<td>3–7 years</td>
<td>↓dysmenorrhea</td>
<td>- Placement (may need sedation or anesthesia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Initial BTB</td>
</tr>
<tr>
<td>DMPA</td>
<td>2</td>
<td>Every 12 weeks</td>
<td>↓dysmenorrhea</td>
<td>- Weight gain in obese adolescents</td>
</tr>
<tr>
<td>Extended OCs</td>
<td>2</td>
<td>Daily tablet</td>
<td>↓dysmenorrhea</td>
<td>- If immobile: VTE risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Daily reminders</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Rx interaction with EI-AED</td>
</tr>
<tr>
<td>POP</td>
<td>2</td>
<td>No E₂ side effects</td>
<td></td>
<td>- BTB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Daily reminders</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Rx interaction with EI-AED</td>
</tr>
</tbody>
</table>

### Jena

- She chose a LNG-IUD because of her desire for optimal bleeding control, highest efficacy, and long duration of action
- Strongly considered use of continuous OCs to reduce rate of hair growth and treatment of acne
- Rejected DMPA: didn’t want further weight gain
- Rejected POP: need for use at same time daily
Newly FDA-Approved Methods of Contraception

Annovera Contraceptive Vaginal Ring (CVR)

Photo credit: Population Council / Hallie Easley
The Basics: Annovera CVR

- Single ring prevents ovulation for one year (13 cycles)
  - Segesterone acetate (Nestorone®) + ethinyl estradiol
  - Used in 28-day cycle; monthly withdrawal (menses)
  - Side effect and bleeding profile similar to NuvaRing
  - Same diameter as NuvaRing, but twice as thick
- Developed by the Population Council
  - Owned by TherapeuticsMD
- FDA approval on August 10, 2018

Comparison of CVRs

<table>
<thead>
<tr>
<th></th>
<th>NuvaRing</th>
<th>Annovera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifespan</td>
<td>1 cycle</td>
<td>13 cycles</td>
</tr>
<tr>
<td>Progestin release rate</td>
<td>Etonogestrel 120 mcg/day</td>
<td>Segesterone 150 mcg/day</td>
</tr>
<tr>
<td>EE release rate</td>
<td>15 mcg/day</td>
<td>13 mcg/day</td>
</tr>
<tr>
<td>Diameter Thickness</td>
<td>54 mm 4 mm</td>
<td>56 mm 8.4 mm</td>
</tr>
</tbody>
</table>

EE: Ethinyl estradiol
The Basics: Annovera CVR

Use of the Annovera CVR

- In place for 21 days, then removed for 7 days to induce scheduled withdrawal bleeding (menses)
- Can be removed for intercourse and cleaning, but not for longer than 2 hours
- Does not require refrigeration
- Water-based vaginal creams and lubricants may be used
- Oil + silicone-based lubricants will alter exposure to EE and segesterone acetate and should not be used

Annovera CVR

- **Efficacy**
  - Phase III trial: 2,308 women at 27 study sites in US, Latin America, Europe, and Australia
    - Women with BMI >29 kg/m² were excluded
  - Of 2,111 females ≤35 years of age, perfect use Pearl Index was 2.98 per 100 woman-years of use
- **Acceptability**
  - Phase 3 study of 905 women: 89% satisfaction rate
  - Related to ease of use, side effects, expulsions/feeling the product and effects during sexual activity
Annovera CVR

• Marketed as the “First woman-controlled, procedure-free, long-acting, reversible birth control product putting the woman in control of both her fertility and menstruation”

• But is it really a “LARC”? 
  – Yes: the description is accurate
  – No: owing to need to remove it monthly and replace promptly after intercourse or cleaning, is not a “forgettable” contraceptive, like an IUD or implant

Annovera CVR

• Commercially available as early as 3rd quarter 2019, commercial release 4th quarter of 2019

• TherapeuticsMD has agreed to provide significantly reduced pricing to Title X family planning clinics

• Not in same FDA contraceptive category as NuvaRing, so must be covered under no cost-sharing rules of ACA
What’s New in Management of Menopause and Perimenopausal Symptoms

Judith M.E. Walsh, MD, MPH
Professor of Medicine
UCSF Women’s Health
Center of Excellence

Conflicts of Interest: None

Overview

• Natural history of menopause
• Hormone therapy: Risks and Benefits
• Menopausal symptoms
• Current role of hormone therapy for menopausal symptoms
• Non-hormonal treatment of menopausal symptoms
MENOPAUSE IS NOT A DISEASE

“Feminine Forever”

- Dr. Robert Wilson, 1966
- Replacing estrogen is like diabetics replacing insulin
- Women “will be much more pleasant to live with and will not become dull and unattractive.”
- Wyeth-Ayerst funded all expenses
Menopause Is A Positive Step

• Gallup poll 1997: Most middle aged American women “welcome menopause as a new and fulfilling life stage.”

• Goal: Support women in achieving a successful transition

Menopause Terms

• Menopause
  – Date of a woman’s final menstrual period (FMP)
  – After FMP, 12 months of amenorrhea

• Menopausal transition (MT)
  – Variability in menstrual cycles before FMP

• Perimenopause
  – Onset of symptoms through one year after FMP
Natural History of Menopause

• Average age is 51
• Predictors of age at menopause
  – Genetics
  – Family history
  – Ethnicity
    • Earlier in Latino and later in Japanese American compared to Caucasians
  – Smoking: about two years earlier
  – Reproductive history
    • Earlier menopause in women never having children and with shorter cycle length

Menopausal Symptoms: Prevalence

• Hot flushes (50% or more)
  • Often with perspiration
• Night sweats (50% or more)
• Sleep disturbance (40-60%)
OTHER SYMPTOMS

• Other symptoms happen at the time of menopause but are less clearly related to menopause
  – Mood changes
  – Cognition
  – Changes in sexual function
  – Urinary complaints
  – Joint pain
Vasomotor Symptoms

- Minnie Pause is a 53 year old woman who had her last menstrual period 18 months ago. She is still having hot flashes and awakens at least twice a night with them. She is considering taking estrogen but wants to know how much longer this will last. What do you tell her?

What do you tell her about when they will go away?

- Average duration is about 2 years and so they should be gone in about 6 months.
- Average duration is about 4 years
- Average duration is about 7 years
- They will never go away
Background

• Treatment for menopausal symptoms is based on their transitory nature
• Many clinical guidelines suggest that symptom duration is approximately 2 years
  – Many studies do not follow women more than 2 years
• Risks and benefits of hormone therapy depend on duration of use
  – “Use lowest dose for shortest duration”
Duration of Vasomotor Symptoms

- Objective: to estimate the natural progression of menopausal symptoms

Vasomotor symptoms

- Rigorous meta-analysis included 10 studies with over 35,000 participants
- Clear definition of vasomotor symptoms
- Assessed prevalence of symptoms and “bothersome symptoms”
Results

• Percent of women with symptoms increased in the two years before the final menstrual period (FMP), peaked one year after the FMP and did not return to premenopausal levels until 8 years after the FMP
• 50% of women had symptoms during the 4 years after FMP
• 10% of women had symptoms up to 12 years after FMP

Results: Bothersome Symptoms
Duration of Vasomotor Symptoms

- Avis NE et al. Duration of menopausal vasomotor symptoms over the menopause transition.
- Objective: to determine total duration of frequent vasomotor symptoms (VMS) during menopause transition, to determine how long frequent VMS persist and to identify risk factors for longer VMS duration
  - JAMA Int Med 2015

SWAN Study

- Multi-ethnic, multi-racial observational study of menopausal transition in 3302 women at 7 sites
  - 13 visits over 17 years
  - Analyses of 1449 women with frequent VMS
- Assessed VMS duration and persistence after FMP
Results

• Median duration of VMS was 7.4 years
  – FMP persistence 4.5 years
• Longer VMS duration in women who were pre or perimenopausal when symptoms began
  – Median 11.8 years
• Women who were postmenopausal when symptoms began had shortest duration
  – Median 3.4 years
• Longer VMS duration
  – African American, younger age, lower educational level, greater perceived stress and symptom sensitivity and higher depressive symptoms and anxiety

Impact

• Frequent VMS lasted more than 7 years for more than half of women
• The earlier VMS started the longer they were likely to last
• This can be included in decision making about menopausal symptom management
Minnie Pause….continued

• Now that Minnie knows that the symptoms could last for a while more, she definitely wants to do something about her intolerable hot flashes. Her only medical history is hypertension well controlled on lisinopril. She would like to hear your thoughts on hormones and whether they are a safe option for her.

• What do you tell her?

What do you tell her?

• Why don’t you try black cohosh- that will work just as well
• Venlafaxine is as effective as hormones and it is a lot safer
• Hormone therapy is probably ok, if you don’t take it for too long
• Absolutely not- no one takes hormones any more
Should I use hormones?

• Ok, so they may help my symptoms…..but are they safe?

Nomenclature

• MHT: Menopausal hormone therapy
• HT: Hormone therapy
• ET: Estrogen therapy
• EPT: Estrogen/progestin therapy
• NOT “HRT”
More Nomenclature

• VMS: Vasomotor Symptoms
• VVA: Vulvovaginal Atrophy
• GSM: Genitourinary syndrome of menopause

Background

• WHI trials designed to determine benefit/risk of hormone therapy when taken for chronic disease prevention
  – Primary efficacy outcome: CHD
  – Primary safety outcome: invasive breast cancer
• Combination trial stopped early due to increased breast cancer risk and unfavorable risk-to-benefit ratio
The News

• *Menopausal Hormone Therapy and Health Outcomes During the Intervention and Extended Post-stopping Phases of the Women’s Health Initiative Randomized Trials*

• Aims:
  – Provide a comprehensive, integrated overview of findings from the 2 WHI hormone therapy trials with extended post-intervention follow-up and stratification by age and other important variables

Methods

• Post-intervention follow up through Sept 30, 2010 based on 81% surviving participants
• Utilized time to event methods based on intention-to-treat, global index calculated
  – CHD, invasive breast cancer, stroke, PE, colorectal cancer, endometrial cancer, hip fracture, and death
Methods

- **Intervention**: 1993-2002 (2004 CEE alone)
- **Extension phase**: 2005-2010
- **Initial WHI**: Randomized to CEE/MPA (or CEE alone) or placebo
  - Instructed to stop study medication
  - Original trial completion date
- **Post-intervention**
- **Post-stopping WHI**: Follow up for those providing additional consent
- **Data in this study**

Results

<table>
<thead>
<tr>
<th>Post-Intervention</th>
<th>CEE + MPA</th>
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<tbody>
<tr>
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<tr>
<td>CHD</td>
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<tr>
<td>Breast CA</td>
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<tr>
<td>All-cause mortality</td>
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<tr>
<td>Global index</td>
<td>4</td>
</tr>
</tbody>
</table>

- Global index HR was not modified by age (p>0.99 for trend)
  - Absolute risks of adverse events were lower in younger than older women
Results

<table>
<thead>
<tr>
<th>Post-Intervention</th>
<th>CEE Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diff/10,000 PY</td>
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</tr>
<tr>
<td>Breast CA</td>
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<tr>
<td>All-cause Mortality</td>
<td>-7</td>
</tr>
<tr>
<td>Global index</td>
<td>-6</td>
</tr>
</tbody>
</table>

- Women in 50s had fewer events per 10,000 PY compared with women in 70s (p for trend, 0.02)

Conclusions

- Neither CEE + MPA nor CEE alone significantly affected all-cause mortality during or after the intervention phase
  - HT has a harmful effect on CHD risk among older women, results in younger women are inconclusive
- Risk–benefit ratio of HT is most favorable when initiated in younger menopausal women
  - Most risks and benefits from hormone therapy dissipate after stopping
The News

- Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women’s Health Initiative Randomized Trials.
  - Manson et al, JAMA 2017

WHI Methods:

**Estrogen + Progestin vs Placebo**
- 16,608 women with a uterus
- Randomized to 0.625mg conjugated equine estrogen + 2.5mg medroxyprogesterone acetate vs. placebo
- On therapy for a median 5.6 years before trial stopped July 2002

**Estrogen-only vs Placebo**
- 10,739 women s/p hysterectomy
- Randomized to 0.625mg conjugated equine estrogen alone vs. placebo
- On therapy for a median 7.2 years before trial stopped February 2004

**Outcome:** All-cause and cause-specific mortality over three time periods:
- cumulative 18 year follow-up,
- mortality during intervention phase, and
- mortality during the post-intervention phase.

Included all deaths reported as of 12/31/2014.

Manson JE et al. JAMA. 2017;381(10):927-938
Results: All-Cause Mortality

• No differences in all-cause mortality during cumulative 18-year follow-up:
  – Estrogen + Progestin
    • 26.4% vs placebo 26.0% (HR 1.02, 95% CI 0.96-1.08)
  – Estrogen alone
    • 28.3% vs placebo 30.0% (HR 0.94, 95% CI 0.88-1.01)
  – Pooled MHT
    • 27.1% vs placebo 27.6% (HR 0.99, 95% CI 0.94-1.03)

• No difference in all-cause mortality during intervention or post-intervention phases

Manson JE et al. JAMA. 2017;381(10):927-938

Results: Cause Specific Mortality

Manson JE et al. JAMA. 2017;381(10):927-938
Results: Breast Cancer Mortality

Manson JE et al. JAMA. 2017;301(10):927-938

MHT and Mortality: Take Home Points

- At 18 years of follow-up, there is no difference in all-cause OR cause-specific mortality between women who took MHT and those who did not.
  - Cancer mortality: no difference
  - CVD: no difference.

- Women can be reassured that treating vasomotor symptoms of menopause with MHT is a safe option for those without contraindications.
Take Home Messages

• For women early in menopause, risks are lowest for hormone therapy and once therapy is stopped these risks wane

• Minnie is young and healthy and would be a candidate for hormone therapy for her vasomotor symptoms; would recommend revisiting the use of hormones annually

ACOG Recommendations

• Management of Menopausal Symptoms, ACOG Practice Bulletin #141: Obstet Gyne. 2014

• Level A Evidence:
  – Systemic HT is the most effective therapy for vasomotor symptoms, low dose has better side effect profile
  – Risks of combined systemic HT include VTE and breast cancer
  – It is recommended that providers individualize care and treat women with lowest effective dose for the shortest duration needed to relieve vasomotor symptoms
Minnie, continued…

- Minnie decides she wants to use hormone therapy and asks what she should start. You have heard that transdermal methods might be safer, but are not entirely sure what to recommend beyond that…

Transdermal Estrogen

- Avoids hepatic first pass metabolism
  - Decreased effect on serum coagulation factors, triglycerides, CRP
- Associated with a lower VTE risk
  » Canonico, 2007
- Associated with a lower risk of stroke
  – Renoux BMJ 2010
- No RCT comparisons of differing HT regimens and clinical CVD outcomes
Key Article

• ACOG Committee Opinion: Postmenopausal Estrogen Therapy: Route of Administration and Risk of Venous Thromboembolism
  – ACOG Committee Opinion #556, April 2013

• Prothrombotic effect of estrogen is possibly related to high concentrations of estrogen in the liver due to first pass effect
• Transdermally administered estrogen has little or no effect in elevating prothrombotic substances

Take home messages

• Transdermal estrogen has been associated with decreased risks of VTE compared with oral forms
• For Minnie, transdermal estrogen is safest, and it may be better to recommend it
  – And she needs a progestin as she still has a uterus
HT for Symptomatic Relief

- Any form of estrogen is highly effective
- Generally can be taken for a few years and gradually stopped
- A progestin should be added for women with a uterus
- Therapy can be tailored to a woman’s preference
- “Lowest dose for shortest duration”

Effective Dose Equivalents

- Dose that stops hot flashes in 80% of women
  - 1 mg micronized 17 beta estradiol
  - 50mcg/day transdermal 17 beta-estradiol
  - 0.625 mg conjugated equine estrogens
  - 1.25 mg piperazine estrone sulfate
Lower dose hormone therapy

- Effective in some trials
- Estimates of efficacy after 12 weeks
  - 38% placebo
  - 63% low dose estrogen
  - 83% standard dose estrogen
- Lower doses may take longer for maximal symptom relief
  - 12 weeks vs 4-8 weeks
- Less bleeding and breast tenderness and may require less progestin

Adding Progestins

- Medroxyprogesterone acetate
  - 2.5 mg daily
  - Micronized progesterone
    - “Natural”
    - 200 mg for 12 days or 100 mg a day
    - Safer for heart and breast?
      - Not proven
- Cyclic vs continuous?
- Levonorgestrel containing IUD?
  - Off label
Bazedoxifene/conjugated estrogen

• Duavee® approved for treatment of menopausal symptoms and prevention of osteoporosis
  – CEE 0.45 mg
  – Bazedoxifene 20 mg
• Bazedoxifene has estrogen agonist effects on bone and antagonist effects on uterine tissue
• Theoretic advantage
  – Relieve estrogen deficiency symptoms while possibly avoiding increased risks of endometrial and breast cancer

Bazedoxifene/conjugated estrogen

• Medication improved indices of vaginal atrophy and reduced daily number of hot flashes compared with placebo
  – (-9 vs -2.4)
• Similar incidence of VTE between groups
• May be useful for women who can’t tolerate progestin
Estee Jenn

- Estee Jenn is a 60 year old woman who has been on HT for 10 years. You have been trying to encourage her to stop it for a while but she has not wanted to do it. Her best friend has recently developed breast cancer; she has now decided to stop, and wants your advice on the best way to do it. What do you recommend?

QUESTION

- Taper by decreasing the daily dose over 6-12 months
- Taper by decreasing the number of days a week HT is used over 6-12 months
- Just stop
Discontinuing hormone therapy

• Symptoms will recur in up to 25% of women with stopping therapy
• Unclear if it is best to stop “cold turkey” or to taper
• Taper can be by daily dose or number of days per week or strength of transdermal estrogen
• Taper until mild symptoms
  – Maintain that dose until symptoms resolve

Factors Associated with Successful Discontinuation of HT

• 2,328 women participated in a survey about HT practices
  – 802/2090 attempted HT discontinuation
• 75% experienced hot flushes after discontinuation
• Factors associated with successful discontinuation: MD advice, lack of symptom relief, vaginal bleeding and learning to cope with symptoms
• Factors associated with unsuccessful discontinuation: trouble sleeping, mood swings or depression

Newton; J Women’s Health 2014
QUESTION

• Estee has a resumption of her hot flashes after she stops her estrogen. What pharmacologic alternative do you suggest?
  – Paroxitene
  – Escitalopram
  – Venlafaxine
  – Clonidine
  – Gabapentin

OTHER DRUG TREATMENTS

• SSRIs
• Venlafaxine
• Desvenlafaxine
• Clonidine
• Gabapentin
• Overall efficacy:
  – 50-67% reduction in hot flash frequency with these regimens
  – Placebo effects generally large
Paroxitene

- Paroxitene CR led to a significant decrease in hot flash score
  - 62% in 12.5 mg group
  - 65% in 25 mg group
  - 38% in placebo group
- Avoid in women receiving tamoxifen
  - Decreases active metabolite of tamoxifen
  - Cytochrome P450 CYP2D6

Brisdelle

- First non-hormonal treatment approved for treatment of menopausal symptoms
  - Paroxitene Salt 7.5 mg
- “Efficacy”
  - Reduced hot flashes/severe hot flashes compared with placebo
  - 1 to 1.7 fewer severe hot flashes per day at different time points
  - Proportion with >50% reduction in moderate to severe hot flashes at 24 weeks
    - 48% vs 36%
Escitalopram

- Reduction in hot flash frequency
  - 55% in escitalopram group
  - 36% in placebo group
- Effective in African American and Caucasian women
- Effective regardless of coexisting anxiety or depression
  - Freeman, JAMA 2011

Venlafaxine

- Significant reduction in hot flashes
  - 61% vs 27% in placebo (p<0.01)
- 150 mg no more effective than 75 mg
  - Lopinzi, Lancet 2000
Venlafaxine vs low dose estrogen

- MsFLASH
- 339 peri and post-menopausal women with at least 2 bothersome VMS per day
  - Low dose estrogen (0.5 mg estradiol)
  - Venlafaxine extended release (75 mg)
  - Placebo
- Mean VMS frequency after 8 weeks
  - Joffe et al JAMA 2014

Results

- Number of VMS per day at 8 weeks
  - Estradiol 3.9 (2.9-4.9)
  - Venlafaxine 4.4 (3.5-5.3)
  - Placebo 5.5 (4.7-6.3)
- Treatment satisfaction highest for estradiol
- Both interventions well tolerated
**Impact**

- Both low dose estrogen and venlafaxine reduced symptoms more than placebo
  - No higher dose estrogen comparison
- Treatment satisfaction with estradiol somewhat higher but clinical significance unclear

**Desvenlafaxine**

- Industry sponsored trial of metabolite of venlafaxine
  - 700 women with severe hot flashes
- 64% reduction in hot flashes at 12 weeks
  - Vs 51% with placebo
- Hot flashes less severe in desvenlafaxine group
- Not currently FDA approved for this indication
  - Speroff, 2008
Clonidine and Gabapentin

- **Clonidine**
  - Start with 0.1 mg/day transdermal patch
  - 40% reduction in hot flashes
  - Side effects can be limiting

- **Gabapentin**
  - 45% reduction in hot flashes vs placebo (29%)
  - 900 mg a day more effective than placebo
  - 300-600 mg at bedtime may help with hot flashes that awaken patients from sleep

“Bioidentical” hormone therapy

- Custom-compounded, multi-hormone regimens
  - Dose adjustments based on serial serum or saliva hormone monitoring
  - No evidence that monitoring is useful

- No evidence it is better than conventional HT
  - Safety not established

- FDA has published statement that the claims are false and misleading
- Endocrine Society states that there is no scientific evidence for bioidenticals
Question

• Estee is tired of medications and would like to try an herbal therapy for treatment of her hot flashes. What treatment do you recommend?
  – Black Cohosh
  – Evening primrose
  – Ginseng
  – Dietary soy
  – Wild yam
  – None of the above

The News

  – Menopause, 2015
• Objective
  – To update and expand the NAMS evidence-based position on nonhormonal management of menopause-associated vasomotor symptoms
Methods

• Systematic review of nonhormonal menopause treatments
• Costs, time, effort and adverse effects weighed against potential effectiveness
• Divided into categories
  – Recommended
  – Recommend with caution
  – Do not recommend at this time

Results

• Recommended
  – Cognitive behavioral therapy and hypnosis
  – Paroxetine is the only FDA-approved non-hormonal treatment
    • Other SSRIs, SNRIs, gabapentin and clonidine have shown efficacy
• Recommend with caution
  – Weight loss
  – Mindfulness-based stress reduction
  – S equol derivatives of soy isoflavones
  – Stellate ganglion block
• Do not recommend at this time
  – Cooling techniques, avoidance of triggers, exercise, yoga, paced respiration, relaxation, OTC supplements and herbal remedies, acupuncture, chiropractic, calibration of neural oscillations
Impact for practice

• When recommending nonhormonal treatments for menopause, clinicians should be aware of the limited evidence supporting them.

• Although many proposed menopause treatments may not have been proven to be beneficial for VMS treatment, some may be relatively benign (e.g. cooling techniques) or have other benefits (e.g. yoga and exercise).

Guidelines for Hormone Therapy Use
**USPSTF Update 2017: MHT and Chronic Disease Prevention**

**Question:** Do benefits outweigh risks for use of MHT in chronic disease prevention?

- Systematic review of 18 RCTS reporting a number of health outcomes:
  - cancer, CHD, dementia, diabetes, fractures, gallbladder disease, stroke, urinary incontinence, VTE, and all cause mortality
  - Divided into Estrogen + progesterone or Estrogen-alone

**Results:** The risks of systemic MHT continue to prevent its use for primary prevention of diabetes, colorectal cancer, or other diseases in the absence of VMS.

-Gartlehner G et al JAMA 2017;318(22

**Recommendations**

- ACOG, AHA, and Canadian Task Force recommend against use of HT for prevention of chronic disease

- NAMS 2012: When alternative therapies not appropriate, extended use of HT appropriate for women at high risk of fracture
NAMS 2017 Position Statement

Vasomotor Symptoms
• Use MHT for women with symptomatic VMS at age <60 or within the first 10 years of menopause
• The lowest doses may take 6-8 weeks for symptoms to improve.
• Non-oral routes of systemic therapy may have improved CV safety, but large, long-term RCTs are lacking.

Genitourinary Symptoms:
• Consider the local estrogen therapy (ET) when non-hormonal therapies fail
• Discuss ET with treating oncologists before prescribing to women who take aromatase inhibitors; systemic absorption with low-dose topical ET is higher than the levels that are typically present with AI use.

NAMS 2017
• “Appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal.
• “Formulation, dose and route of HT should be determined individually and reassessed periodically”
• Replaces “lowest dose for shortest duration”
NAMS Recommendations for Older Women (2015)

- Provided that the woman has been advised of the increase in risks associated with continuing HT beyond age 60 and has clinical supervision, extending HT use with the lowest effective dose is acceptable under some circumstances, such as for the woman who has persistent bothersome menopausal symptoms and for whom her clinician has determined that the benefits of menopause symptom relief outweigh the risks.
  - Use of HT should be individualized and not discontinued solely based on a woman’s age.
  - Decision to continue or discontinue should be made jointly.

Donna

- Donna is a 67 year old woman with significant vaginal atrophy. She has not been sexually active for some time and when asked if this is bothersome to her she admits it causes difficulties in her relationship with her husband. She is very hesitant to use hormones in any form because she reads a lot of articles about them and doesn’t think they are safe. She has significant pain with intercourse, no other major symptoms.

- What recommendations do you have?
What do you tell her?

- Vaginal moisturizers
- Estrogen crème will work and it is safer than the pills
- Why don’t you try an estrogen vaginal ring? It’s safer than the crème
- There is a medication called ospemifene that could help

Genitourinary Syndrome of Menopause

- Vaginal changes
  - Vaginal spotting or bleeding, dryness
- Dyspareunia: poor lubrication, less vaginal elasticity, skin irritation, introital shrinkage
  - Negative impact on relationships and quality of life
- Bladder and urethra changes
  - Urgency, frequency, dysuria, urge incontinence
  - No effect on stress incontinence or pelvic organ prolapse
Background

• GSM is associated with physical discomfort, sexual dysfunction, emotional distress, and reduced quality of life
• Incidence of GSM can be ~60%
  – Less than 10% of women state that provider initiated a conversation
• Usual treatment options have been estrogen or vaginal moisturizer

Treatment Options

• Vaginal moisturizers are used several times a week and vaginal lubricants are used for sexual intercourse
  – Moisturizers: Replens, Vagisil
  – Lubricants: Astroglide, K-Y Jelly, Elegance Women’s
• Can improve symptoms of vaginal dryness or coital comfort but do not reduce vaginal atrophy
Local Estrogen

• Most effective treatment for moderate to severe symptoms related to vaginal atrophy
• Can also reduce UTIs and symptoms of overactive bladder
• Typically given daily initially and then twice a week

Local Estrogen Preparations

• Creams
  – Estradiol (100 µcg/g) or CEE (0.625 mg/g)
  – 1 applicator qd for 7 days
  – Then ¼ to ½ applicator twice a week
• Tablet
  – Vagifem (10 µcg estradiol)
  – 1 tab vaginally for two weeks then one tab twice a week
• Ring
  – Estring
  – Releases 7.5 µcg estrogen daily for 90 days
Ospemifene

- Novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy
- Trial in over 600 women with moderate to severe dyspareunia
- Severity of vaginal pain improved by 2-3 levels in 52.8% of ospemifene, 38.8% of placebo
- Hot flushes were the most common AE
  - Only 4.6% in treatment group discontinuing due to AE

DHEA (prasterone)

- Treatment option for dyspareunia associated with VVA
- Daily vaginal suppository
- Has not been directly compared with estrogen
- Slight increase in circulating testosterone, estrone and DHEA
Laser or energy based devices

• Not FDA approved
• Observational evidence encouraging but RCTs are needed
• Safety Warning July 2018
  – May need to adverse events including vaginal burns, dyspareunia

Complementary therapies

• Oral Vitamin D?
• Vaginal Vitamin E?
• Oral and vaginal probiotics to alter the vaginal microbiome?
GSM Treatments

- Start with lubricant with intercourse and vaginal moisturizer [*Level A*]
- Mod-severe symptoms: low dose vaginal estrogen or ospemifene [*Level A*]
  
  - NAMS, 2014

Take Home Messages

- Screen women for dyspareunia and VVA—it’s common and distressing for women
- Ospemifene is a SERM with apparent positive effects on VVA without endometrial or VTE events
  - Vasomotor symptoms are the most common side effect
  - Not for use in women with a history of breast cancer
  - FDA approved for moderate-severe dyspareunia
Treatment of GSM

- Regular sexual activity helps maintain vaginal health
- Start with moisturizers and lubricants
- Vaginal Estrogen if moisturizers and lubricants are insufficient
  - Type of estrogen dependent on patient preference
- Ospemifene if a woman can’t (arthritis, obesity, vulvodynia) or prefers not to use vaginal product

Women with Breast Cancer

- Topical estrogen has minimal systemic absorption but it is not zero
- Start with non-hormonal options
- Women on aromatase inhibitors
  - Probably best to avoid
- Women with low risk of recurrence
  - Probably ok
  - In concert with oncologist and with discussion of pros and cons
Summary

- Average duration of menopausal symptoms is approximately 4-7 years but seems to be longer in younger women
- Estrogen either alone or with a progestin is not recommended for chronic disease prevention in postmenopausal women
- Risks and benefits of estrogen treatment may differ in older and younger women

Summary

- Estrogen works best for symptoms
  - Continued periodic reassessment
- Best method for discontinuation is not known
- Start with lifestyle modifications and nonprescription remedies
- Drug alternatives include SSRIs, SNRIs, gabapentin, clonidine and combined estrogen/SSRI
Genitourinary Syndrome

- Regular sexual activity, moisturizers and lubricants
- Topical estrogen: start with higher dose and then decrease to maintenance dose
- Ospemifene: for women who can’t or won’t use estrogen
- Women with breast cancer individualized decision
Questions?
CHRONIC KIDNEY DISEASE UPDATE: WHAT THE GENERALIST NEEDS TO KNOW

MICHAEL G. SHLIPAK, MD, MPH
SCIENTIFIC DIRECTOR, KIDNEY HEALTH RESEARCH COLLABORATIVE
PROFESSOR OF MEDICINE, EPIDEMIOLOGY & BIOSTATISTICS
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
ASSOCIATE CHIEF OF MEDICINE FOR RESEARCH DEVELOPMENT
SAN FRANCISCO VA MEDICAL CENTER

August 8, 2019

Disclosures

- I am on the Scientific Advisory Boards with stock option compensation for the following companies:
  - TAI Diagnostics
  - Cricket Health, Inc.
Outline

- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Introduction to Cystatin C
- Treatment of CKD
- Hyperkalemia
Question 1: Which of these patients has CKD?

a) Heart failure patient in ED with creatinine of 2.0
b) Diabetes patient with albumin/creatinine of 100 mg/g, creatinine= 1.0 mg/dL
c) 35 year old African American man with creatinine of 1.5
d) All of the above

DEFINITION & CLASSIFICATION OF CHRONIC KIDNEY DISEASE

KDIGO 2012 Clinical Practice Guideline (CPG) for the Evaluation and Management of Chronic Kidney Disease

Introduction

- **Chronic Kidney Disease (CKD):**
  - Defined in 2002 with original CKD staging
  - Replaced earlier terms “chronic renal insufficiency”, “chronic renal failure”, or “high creatinine”
  - Previous 5 CKD stages were developed by an expert panel
  - Most CKD epidemiology research has been conducted since the 5 stages were defined

Definition and Complications

- **Overall CKD definition unchanged**
- **Chronic kidney disease:** >3 month duration of either:
  - Decreased kidney function (GFR<60)
  - Injury/damage to the kidney (e.g. albuminuria, cysts, stones)
- **Etiology of CKD:**
  a) **Common diseases treated by generalists:** diabetes, hypertension, cardiovascular disease, heart failure
  b) **Other systemic diseases typically treated by specialists:** systemic lupus erythematosus, HIV, urological diseases
  c) **Primary kidney disease:** polycystic kidney disease, glomerular disease
Complications of CKD

- Kidney failure (end-stage renal disease)
- Death

Other chronic disease:
- Atherosclerotic Cardiovascular Disease
- Heart failure
- Osteoporosis/fracture
- Cognitive impairment/dementia
- Frailty

Treatment Complications:
- Medications
- Procedures

Prognosis by eGFR and Albuminuria

- Key meta-analysis published in 2010 in Lancet
- Evaluated prognosis by eGFR and albuminuria
- 21 studies, 1.2 million patients

- Predictor:
  - eGFR categories
  - Albuminuria (ACR categories)
- Outcome: mortality risk
### Albuminuria and eGFR grid


<table>
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<tr>
<th>Albuminuria Classes (mg/g)</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-300</th>
<th>&gt;300</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR</strong> (mL/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;105</td>
<td>1.0</td>
<td>1.4</td>
<td>2.0</td>
<td>4.4</td>
<td>1.2</td>
</tr>
<tr>
<td>90-104</td>
<td>1.0</td>
<td>1.3</td>
<td>1.5</td>
<td>3.1</td>
<td>1.0</td>
</tr>
<tr>
<td>75-89</td>
<td>0.9</td>
<td>1.2</td>
<td>1.7</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>60-74</td>
<td>0.9</td>
<td>1.2</td>
<td>1.8</td>
<td>3.0</td>
<td>1.3</td>
</tr>
<tr>
<td>45-59</td>
<td>1.2</td>
<td>1.5</td>
<td>1.9</td>
<td>3.4</td>
<td>2.0</td>
</tr>
<tr>
<td>30-44</td>
<td>1.7</td>
<td>2.1</td>
<td>3.0</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>15-29</td>
<td>4.0</td>
<td>3.0</td>
<td>4.2</td>
<td>6.0</td>
<td>3.6</td>
</tr>
<tr>
<td>All</td>
<td>1.0</td>
<td>1.3</td>
<td>2.0</td>
<td>3.6</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05


### ESRD Risk

**ESRD Risk**

**Kidney Failure Equation: kidneyfailurerisk.com**

<table>
<thead>
<tr>
<th>Albuminuria Classes (mg/g)</th>
<th>&lt;10</th>
<th>10-29</th>
<th>30-300</th>
<th>&gt;300</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>eGFR</strong> (mL/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;105</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>90-104</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>75-89</td>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>60-74</td>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>45-59</td>
<td>0.1</td>
<td>0.8</td>
<td>1.4</td>
<td>5.3</td>
<td>0.3</td>
</tr>
<tr>
<td>30-44</td>
<td></td>
<td></td>
<td></td>
<td>9.2</td>
<td></td>
</tr>
<tr>
<td>15-29</td>
<td></td>
<td></td>
<td></td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05

Outline

- Definition and Complications
- New CKD Staging 2013
- Screening for CKD
- Introduction to Cystatin C
- Treatment of CKD
- Hyperkalemia

CKD Stages and Prevalence

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Estimated GFR (mL/min per 1.73 m²)</th>
<th>U.S. Prevalence N (1000's) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD Stage 1</td>
<td>90+&lt;sup&gt;*&lt;/sup&gt;</td>
<td>3,200 (1.6)</td>
</tr>
<tr>
<td>CKD Stage 2</td>
<td>60-89&lt;sup&gt;*&lt;/sup&gt;</td>
<td>6,500 (3.2)</td>
</tr>
<tr>
<td>CKD Stage 3</td>
<td>30-59</td>
<td>15,500 (7.7)</td>
</tr>
<tr>
<td>CKD Stage 4</td>
<td>15-29</td>
<td>700 (0.4)</td>
</tr>
<tr>
<td>CKD Stage 5</td>
<td>&lt;15 (or dialysis)</td>
<td>400 (0.2)</td>
</tr>
</tbody>
</table>

<sup>*</sup>With evidence of kidney damage, e.g. albuminuria

KDOQI Guidelines, AJKD, Feb. 2002
Problems with Old Staging

- Stages 1 and 2 were the same
- Stage 3 (30-60) was too broad; eGFR of 30-45 is very different from 45-60
- Did not address levels of albuminuric; and only used albuminuria for Stages 1 and 2

From Old to New Staging

<table>
<thead>
<tr>
<th>Cause</th>
<th>eGFR (mL/min per 1.73 m²)</th>
<th>Albuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>G1 (&gt;90)</td>
<td>A1 (ACR &lt; 30)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>G2 (60-89)</td>
<td>A2 (ACR 30-300)</td>
</tr>
<tr>
<td>Polycystic Disease</td>
<td>G3a (45-59)</td>
<td>A3 (ACR &gt; 300)</td>
</tr>
<tr>
<td>Unknown</td>
<td>G5 (&lt; 15)</td>
<td></td>
</tr>
</tbody>
</table>

| CKD Stage 3 GN               | 30-59                      | 15,500 (7.7) |
| CKD Stage 4                  | G4 (45-59)                 | 700 (0.4)    |
| CKD Stage 5                  | <15 (or dialysis)          | 400 (0.2)    |
**CGA Staging for CKD**

- It is recommended that CKD be classified by:
  - **Cause**
  - **GFR category**
  - **Albuminuria category**


---

**Outline**

- Definition and Complications
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- **Screening for CKD**
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Screening for CKD

- International CKD guidelines do not address when or how to screen
  - No RCT evidence for or against
  - Relative costs of screening vary by region
- Hypertension, Diabetes, and CVD guidelines all recommend some form of CKD screening.
- The following are my suggestions for primary care:

Who to Screen with Urine Albumin?

- Primary prevention screens:
  - Diabetes- annual
  - Hypertension
  - Elderly
- CKD Staging:
  - Urine albumin is now important part of CKD staging
  - Should be measured and documented in all CKD patients
    - Repeat annually in diabetics
    - every 2-3 years in non-diabetics
How to Measure Urine Albumin

- Often listed as “microalbumin panel”
- Focus on albumin/creatinine ratio (ACR):

<table>
<thead>
<tr>
<th>ACR (mg/g)</th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30</td>
<td>Normal</td>
<td>Normal or mildly elevated</td>
</tr>
<tr>
<td>30-300</td>
<td>Microalbuminuria</td>
<td>Moderately elevated</td>
</tr>
<tr>
<td>&gt;300</td>
<td>Macroalbuminuria</td>
<td>Severely elevated</td>
</tr>
</tbody>
</table>

- Dipstick: “trace” is abnormal
- If dipstick is abnormal, quantify ACR

Who and When to Check Creatinine?

- Begin screening:
  - Age >40 lower-risk populations
  - Age >30 Blacks, Native Americans
- Diagnosis of hypertension, diabetes, cardiovascular disease, heart failure
- Frequency of creatinine monitoring (no evidence)
  - No risk factors: 3-5 years
  - Risk factors: 1-2 years
- Creatinine cost: $0.20
Question 3: Which of the following is true about creatinine GFR estimates?

a) More accurate in older populations than middle-aged because prevalence of kidney disease is higher
b) They have been validated in most ethnic groups
c) They are more likely to be accurate in healthy persons than in persons with chronic illness
d) All of the above

GFR Estimation from Creatinine

- **Estimated GFR:**
  - Automatic reporting by most labs
  - Equations are rough
  - <60 concerning for kidney disease, but not specific
  - >60- so imprecise, its considered just “>60”

- **3 equations in current use:**
  - Cockroft-Gault (Nephron, 1976)- used by FDA and pharmacies
  - MDRD (Annals, 1999)- used for most automated reporting
  - CKD-EPI (Annals, 2009)- favored by researchers
Pros and Cons of Estimated GFR

**Pros:**
- Indexes creatinine for demographic characteristics
- Forces us to think in terms of GFR and kidney function

**Cons:**
- Mostly validated in younger patients with kidney disease
- Huge assumption that demographic characteristics alone can define muscle mass
- Only developed in Whites and Blacks
- Estimated GFR ≠ GFR

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- **Introduction to Cystatin C**
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**Question 4: Which of the following is true of cystatin C?**

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>Better marker of GFR than creatinine</td>
</tr>
<tr>
<td>b)</td>
<td>Better marker of glomerular injury than albumin</td>
</tr>
<tr>
<td>c)</td>
<td>Has not been studied in African Americans, but approved for use in Whites</td>
</tr>
<tr>
<td>d)</td>
<td>Only used outside the U.S.</td>
</tr>
<tr>
<td>e)</td>
<td>All of the above</td>
</tr>
</tbody>
</table>

---

**Cystatin C**

- Cystatin C is a blood test of kidney function that is an alternative better version of creatinine.
- Because cystatin C is not related to muscle mass (or age, sex, and race), it has major advantages over creatinine.
- Cystatin C is a reliable, standardized, and automated measure that is available for clinical use.
“Cystatin C versus Creatinine in Determining Risk based on Kidney Function”
Shlipak et al. New England Journal of Medicine, 2013

- Meta-analysis of all available observational studies and clinical trials with creatinine and cystatin C
- 16 studies, 90,750 persons
- Compared associations of eGFRcr, eGFRcys, and eGFRcr-cys with mortality risk
- Determined proportions reclassified by cystatin C in each eGFRcr subgroup and impact on risk associations
Comparisons of eGFR Using Creatinine, Cystatin C, or both with All-Cause Mortality


Reclassification by eGFRcys and associated risk

Adjusted for age, gender, race, smoking, systolic blood pressure, total cholesterol, diabetes, history of cardiovascular disease, body mass index, and albuminuria.
International Guidelines Support Use of Cystatin C


KDIGO Suggestion #1 (2B)

- Estimating GFR:
  1. Use creatinine eGFR
  2. Are you confident that this is accurate?
  3. If not, use either:
     - Cystatin C
     - Direct measure GFR
KDIGO Suggestion #2 (2C)

**Confirming CKD:**

Your patient’s eGFRcr is 45-60 and is not known to have kidney disease:
- Measure cystatin C
- If cystatin C eGFR <60: patient has CKD
- If cystatin C eGFR >60: patient does NOT have CKD

KDIGO Recommendation (1C)

- For medical dosing of potentially toxic agents, use cystatin C or direct measure GFR
- Potential examples – newer oral anti-coagulants, chemotherapeutics, metformin
- Major challenge – FDA has dosing based on creatinine clearance
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CKD Treatment

- Goals:
  - Prevent progression to ESRD
  - Prevent CKD complications

- Treatments:
  - ACE/ARB therapy
  - Blood Pressure Control
  - Glucose Control in Diabetes
  - Statins
ACE/ARB’s in Diabetic and Non-Diabetic CKD

Shlipak, Clinical Evidence 2009

- Diabetic CKD- nearly always has albuminuria
- Diabetic CKD- ACE/ARB essential for:
  - Moderate albuminuria (ACR 30-300)
  - Severe albuminuria (ACR > 300)
- ACE/ARB’s do not appear to be helpful to prevent onset of albuminuria
- In non-diabetic CKD, ACE benefit limited to persons with proteinuria
  - Rahman M, Arch Intern Med, 2005

Conclusion: For patients with reduced eGFR but normal levels of albuminuria - choice of blood pressure agent probably does not matter

Frequently Asked ACE/ARB Questions

- **Question 1:** How much increase in creatinine is safe?
  - **Answer 1:** ↑ of creatinine >30% is common; worry about the potassium

- **Question 2:** Do we stop the ACE in advanced CKD?
  - **Answer 2:** Only if the potassium is un-manageable
    
    *RCT: Hou FF et al. NEJM 2006; 354: 131-140*

- **Question 3:** Is there a reason to combine ACE + ARB?
  - **Answer 3:** No, might decrease proteinuria, but increased potassium risks too high
    
    *Mann JF et al. Lancet, 2008*
Blood Pressure Target Uncertain in CKD

- Modern RCTs HAVE NOT proven that tighter BP control reduces CKD PROGRESSION
- Guidelines controversial around BP targets with recent AHA/ACC guideline target of <130mmHg based upon the SPRINT trial

Does SPRINT apply to CKD patients?

- SPRINT Trial: SBP <120 (Intensive) vs. <140 (Standard)
- Primary Outcome (CVD composite): HR 0.75 (0.64 – 0.89)
- CKD subset (N = 2,646)
  - Primary CVD outcome: 0.82 (0.63-1.07) (interaction p=0.36)
  - ESRD or 50% lower eGFR: 14 vs. 15 events
- Summary: Impact of intensive BP lowering appear similar in persons with or without CKD.
- Participants without CKD at baseline had higher incidence of CKD (127 vs. 37 events)
  - These cases of new CKD do not appear to represent actual injury to the kidney
Glycemic Control in Diabetic CKD

- **Type I Diabetes**: tight glucose control slows kidney disease progression: OR = 0.34 (0.20-0.58)

- **Type II Diabetes**: ADVANCE trial *(NEJM, 2008, 2560-72)*
  - Tight glucose control (HbA1c 6.5 vs. 7.3): 20% lower risk of “new or worsening nephropathy” (RR 0.80; p=0.006)
  - Low rates: 4.1% vs. 5.2%

- In Type II Diabetes, risks of tight glucose control probably offset kidney benefits in older patients.

Statins in CKD- beneficial for CVD

- Statins lower CVD risk in CKD patients:
  - Meta-analysis of 20 early studies (N=18,746 patients) found RR 0.80 (95% CI: 0.70,0.90)
  - SHARP RCT: (N=9,500) simvastatin/ezetimide vs placebo RR= 0.83 (95% CI: 0.74-0.94)

- No effect on CKD progression

- No benefits of statins in patients with ESRD
Question 5

In a stable patient on an ACE or ARB, I will tolerate K levels up to the following without stopping the ACE/ARB:

a) 5.1
b) 5.3
c) 5.5
d) 5.9

Question 6

Your patient with diabetic nephropathy (eGFR<40, ACR 150) has serum K of 5.3 on repeat measures over 6 months. She is asymptomatic and has a normal physical exam except for symmetric decreased sensation to the ankle. What should you do next?

a) Change to losartan as it causes less hypokalemia
b) Increase her furosemide to lower the K
c) Educate her about situations that would elevate her K further
d) Stop the lisinopril
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A New Era for the Treatment of Hyperkalemia?

*Hyperkalemia is in the Eye of the Beholder*

- Mild hyperkalemia: 5.0-5.9
- Moderate hyperkalemia: 6.0-7.0
- Severe hyperkalemia: >7.0
New Agent to Treat Hyperkalemia in CKD (Patiromer)  
Weir MR, NEJM 2015

- FDA approved
- Subjects: CKD and mild/moderate hyperkalemia (5.0-5.6)
  - eGFR: 38
  - K: 5.6
- Intervention: patiromer (4.2g or 8.4mg BID)
- Adverse effect: constipation – 11%

Baseline: 5.7  
Day 3: 5.2  
1 week: 4.9

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>249</td>
<td>237</td>
<td>228</td>
<td>221</td>
<td>210</td>
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<tr>
<td>Mild hyperkalemia</td>
<td>92</td>
<td>80</td>
<td>76</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>151</td>
<td>137</td>
<td>141</td>
<td>136</td>
<td>114</td>
</tr>
</tbody>
</table>

Thank you!  
Any Questions?
UCSF Essentials of Primary Care Conference
Squaw Creek, CA
August 8, 2019

Maximizing Skills in Office
GYN Procedures

Michael S. Policar, MD, MPH
Professor Emeritus of Ob, Gyn, and Repro Sci
UCSF School of Medicine
michael.policar@ucsf.edu

Disclosures

• Bayer Healthcare
  – Litigation consultant (expert witness)

• Sebela Pharmaceuticals
  – Investigator proctor in phase III trial of a copper IUD (VeraCept)
Outline

• Pain relief for office procedures
• Endometrial biopsy
• Vulvar biopsy
• Bartholin duct and vulvar abscesses
• Vaso-vagal syncope
• IUD challenges
• Contraceptive implant challenges

Mary 18 Year Old G₀ P₀
“I Am So Afraid to Have This Done!”
Outpatient Procedure Pain Relief
Principles And Application

- Pre-insertion NSAIDs
- Verbicaine (aka: vocal local)
- Slow technique
- Tenaculum site local anesthetic
- Tenaculum and sound technique
- Paracervical and intracervical block

Non-Steroidal Anti-inflammatory Drugs

Cochrane review, 2015
- Tramadol and naproxen had some effect on reducing IUD placement pain in specific groups
- Lidocaine 2% gel, misoprostol, and most NSAIDs did not help reduce pain

• Conventional wisdom
  – Rx naproxen sodium 550 mg or Ibuprofen 800 mg
  – Helps mainly with post-placement cramping

Verbicaine

• Keep her talking!
• Calm, soothing vocal tone
• Slow, easy pace

• Utilize whatever works for the patient **ASK**
  • Breathing techniques
  • Mindful mediation
  • Guided imagery

Distraction
“Most patients are worried about pain, and they are often surprised when it is easier than they had expected. As we proceed, let us know how you are feeling so that we can make adjustments. We want this to go well for you.”

Language Considerations

Instead of:

“Relax”

You might feel “a pinch” or “a stick and a burn”

“You’re doing great”

Try:

“Try taking a deep breath”

“It’s a natural reaction to lift up. See if you can let your hips be heavy on the table.”

“You might feel a sensation or “a twinge”

“I can see you’ve had practice with relaxation”
**Language Considerations...**

**Instead of:**
- I’m going to put a grasper on your cervix
- Now I’m going to sound your uterus
- Here comes the inserter

**Try:**
- “You may notice three cramps, then we’ll be done”
- Let me know if you want me to tell you before each one

---

**Tenaculum**

**Choose Site for Placement**

- Anterior lip
- Posterior lip
- Typically a horizontal bite, some prefer vertical

**Do not occlude os!**
Tenaculum: Size of Bite

- 1-1.5 cm wide
- 1 cm deep
- Not too shallow- may tear through
- Not too deep- unnecessary

Tenaculum Pain Reduction

- Once the teeth are in contact with the cervix, press into the tissue
- Close the tenaculum very, very slowly
  - Only to the first or second stop
  - Silently
- Once the ratchet is closed, test your application gently to be sure it is secure
**Tenaculum Pain Reduction**

- Some providers recommend injection of 1cc local anesthetic at the tenaculum site
  - Have patient cough or use other distraction
- Don’t move the tenaculum inadvertently
- Hook fingers thru rings to place tenaculum
- During sounding and IUD placement, don’t hook your fingers through the rings...hold the shank

**Tenaculum Use When Sounding**

- Change hands; hold the tenaculum with the non-dominant hand while sounding and for placement
- OK to let tenaculum lay on speculum when picking up the sound or IUD
- Thumb on one side of ratchet; fingers on the other
  - Avoid the rings
  - Avoid inadvertent movements
**Uterine Sound: Purpose**

- Ensure that you can pass through the internal os
- Direction and pathway through the os to the fundus
- Measures depth/distance from external os to fundus
  - Appropriate for IUD placement not <5.5 cm
  - 10 cm or more in some cases
  - Tells you where to set the flange
  - So you don’t waste the IUD

**Uterine Sound Pain Reduction**

- If metal; bend sound to mimic uterine flexion
- Hold it like a pencil or dart
- Use *wrist* action
  - Not elbow
  - Not shoulder
- Brace fingertips on speculum to achieve control of force while advancing the sound
Uterine Sound Pain Reduction

**S-l-o-w Progression**

- Through the internal os
- *Pause once when through the internal os*
- Slow intentional progression to the fundus
- Avoid momentum

---

**Uterine Sound Pain Reduction**

- Touch the fundus once
  - Repeated tapping is unnecessarily uncomfortable for the patient
- Move slowly and intentionally
  - Moving too quickly increases discomfort
- If difficulty sounding, consider
  - EMB sampler
Still Unable To Pass Through Internal Os

- Place paracervical or intracervical block at any point
- Use a thinner sound (endometrial sampler)
- Use os finder device
- Dilate internal os with small metal or plastic dilator
- Try a shorter wider speculum
- Reposition the tenaculum onto a different place
- If unsuccessful, return after misoprostol 200 mg per vagina 10 hours and 4 hours prior to placement

Os Finder Device

Cervical Os Finders (Disposable Box/25)
Cervical Os Finder Set (Reusable Set of 3)
Dilators

- Dilate internal os with metal dilators
- #13 french
  - Divide by 3.16 to get mm (4.1 mm)
- Double ended
- Tapered ends ease passage through os

Passed Through with Sound
...But not the inserter!

- Choke up on the handle
- Sterile lubricant on tip
- Leave the (small) sound in the canal and come alongside the sound with the inserter
Cervical Anesthesia

10-20 ml of 1% lidocaine (NO epinephrine)

Mody et al. ObGyn 2018
Pain with IUD Insertion, Nulliparas

10 mL

Akers et al. ObGyn 2017

Paracervical Block

- Target is uterosacral ligaments, which contain the cervical and uterine nerves
- Use spinal needle OR 25g, 1 ½” needle + extender
- Inject at reflection of cervico-vaginal epithelium
Paracervical Block

- 5-10 cc 1% lidocaine (no epinephrine) each side
- Submucosal injection 5mm-1cm deep
- Short speculum allows more movement
- WAIT 1-2 minutes after placing block
Paracervical Block

- Targets the paracervical nerve plexus
- 1 ½ inch 25g needle with 12 cc “finger lock” syringe
- Inject ½- 1 cc. at 12 o’clock, then apply tenaculum

Intracervical Block

- Targets the paracervical nerve plexus
- 1 ½ inch 25g needle with 12 cc “finger lock” syringe
- Inject ½- 1 cc. at 12 o’clock, then apply tenaculum
Intracervical Block

- Angulate needle at the hub to 45° lateral direction
- At 3 o’clock, insert needle into cervix to the hub 1 cm lateral to external os, then aspirate
  – Inject 4 cc of local, then 1 cc while withdrawing
- Rotate barrel 180°, then inject at 9 o’clock
Lidocaine Safety

- Inject in correct spot
- Aspirate to avoid intravascular injection
- Metallic taste is a common side effect

Maximum Local Anesthetic Dosing

<table>
<thead>
<tr>
<th>Local Anesthetic</th>
<th>Onset (mins)</th>
<th>Max Dose (mg/kg)</th>
<th>Max Dose (mg) without/with epi</th>
<th>55kg pt dose without/with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>4-7</td>
<td>4.5/7 mg/kg</td>
<td>300/500 mg</td>
<td>25/38 mL</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>10-20</td>
<td>2.5 mg/kg</td>
<td>175 mg</td>
<td>55 mL</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>fast</td>
<td>11/14 mg/kg</td>
<td>800/1000 mg</td>
<td>60/77 mL</td>
</tr>
</tbody>
</table>

- Rough estimates that are not evidence-based
- Lower peak levels and slower absorption with vasoconstrictor
- Adding bicarb (to lidocaine) speeds onset of action
- Bupivacaine with less difference since med is vasoconstrictive
Endometrial Biopsy

Who Needs an EMB?

- **Purpose:** detect endometrial hyperplasia or cancer
- **Menopausal woman**
  - Any postmenopausal bleeding, if not using HT
  - Unscheduled bleeding on continuous-sequential hormone therapy
  - Bleeding > 3 mo after start of continuous-combined hormone therapy
  - Endometrial stripe > 5 mm (applies to postmenopausal woman only)
  - Pap smear: *any* endometrial cells or AGC Pap
Who Needs an EMB?

Premenopausal Women

- Prolonged metrorrhagia
- Unexplained post-coital or intermenstrual bleeding
- Endometrial cells on cytology in an anovulatory premenopausal woman
- Atypical Glandular Cells (AGC) cervical cytology
  - Abnormal endometrial cells, or
  - Older than 35 years old
  - Under 35 yo with abnormal bleeding

Technique of EMB

- Bimanual exam to evaluate uterine axis, size
- Cleanse cervix with antiseptic
- S-l-o-w-l-y apply tenaculum (+ local anesthetic)
- Use of the sampling device
  - Choose correct type (rigidity) of sampler
  - “Crack” stylet to ensure easy movement
  - Gently advance to fundus; expect resistance at internal os
  - Note depth of sounding with side markings
  - Pull back stylet to establish vacuum
Technique of EMB

- **Use of the sampling device (continued)**
  - Rotate in a helical direction from the fundus to the os in order to use the *lateral cutting edge* of the port
  - If the sampler has filled, remove → place tissue in fixative
  - If the sampler did not fill, repeat 2-3 more passes
  - If a “curette check” for completeness is desired, perform in-and-out motion in vertical strips to confirm a “gritty” feel
  - Cut tip of sampler and empty any remaining tissue
- Remove the tenaculum; check for bleeding
- Remove the speculum
- Move the patient to a supine position for a few minutes
Tips for Internal Os Stenosis

- **Pain relief**
  - Use para-cervical or intra-cervical block
  - Intrauterine instillation of lidocaine

- **Cervical dilation**
  - Freeze endometrial sampler to increase rigidity
  - Grasp sampler with ring forceps 3-4 cm from tip
  - Use cervical “os finder” device
  - Use small size Pratt or Hegar dilators
  - *No evidence to support misoprostol priming*

Indications for Vulvar Biopsy

- Papular or exophytic lesions, except obvious condylomata
- Thickened lesions (biopsy thickest region) to differentiate VIN vs. LSC
- Hyperpigmented lesions (biopsy darkest area), unless obvious nevus or lentigo
- Ulcerative lesions (biopsy at edge), unless obvious herpes, syphilis or chancroid
- Lesions that do not respond or worsen during treatment
- *In summary*: biopsy whenever diagnosis is uncertain
Vulvar Biopsy

Tools for Vulvar Biopsy

- Insulin syringe
- 1% lidocaine with or without epinephrine
- 2x2 or 4x4 gauze sponge
- Unsterile exam gloves
- Antiseptic solution (e.g., povidone-iodine or chlorhexidine)
- Silver nitrate sticks or Monsel’s solution
- Pathology container and label

Photo courtesy of Dr Hope Heafner
Tips for Vulvar Biopsies

• Where to biopsy
  – Homogeneous: one biopsy in center of lesion
  – Heterogeneous: biopsy each different lesions

• Prep skin with antiseptic

• Skin local anesthesia
  – Most lesions will require ½ cc. lidocaine or less
  – Epinephrine will delay onset, but longer duration
  – Use smallest, sharpest needle: *insulin syringe*
  – Inject anesthetic s-l-o-w-l-y

• Alternative: 4% liposomal lidocaine (30 minutes) or EMLA (60 minutes) pre-op

• Stretch skin; twist 3 or 4 mm Keyes punch back-and-forth until it “gives” into fat layer
Tips for Vulvar Biopsies

• Lift circle with forceps or needle; snip base
• Hemostasis with AgNO₃ stick or Monsel’s solution
  - Silver nitrate will not cause a tattoo
  - Suturing the vulva is almost never necessary
• Separate pathology container for each area biopsied
• LABEL the container!!!

Bartholin Duct and Vulvar Abscess Management
Bartholin’s Duct and Gland Conditions

- 2% lifetime risk of developing BD cyst or abscess, especially during reproductive years
- BD abscess is 3-times more common than BD cyst
- If duct becomes blocked or transected
  - No infection: BD cyst
  - Primary infection: acute BD cellulitis or abscess
  - Rarely, BD cyst is secondarily infected → abscess
  - All surgical treatments are designed to drain fluid and create a new duct
- BG/BD carcinoma is rare; occurs in women > 40 yo
Bartholin Duct Cellulitis
(aka: Bartholinitis, Bartholin adenitis)

- Painful red induration of lateral perineum at 5 or 7 o’clock, but no palpable abscess
- Most commonly due to skin streptococcus
- Treatment
  - Cephalexin 500 mg PO QID or
  - Clindamycin 300-450 mg PO QID
  - 5 day course, but extend if not improved (IDSA #15)
  - Moist heat: sitz baths, warm compresses

Re-evaluate in 2-4 days
- Cellulitis will either have improved or point as abscess
- If abscess develops, perform I&D
- Admit immunocompromised women (especially diabetics) for IV antibiotics and close observation
- Risk of developing necrotizing fasciitis
Bartholin Duct Abscess

- Develops over 2-4 days; up to 8 cm diameter
- Tend to rupture and drain after 4-5 days
- Pain may range from local discomfort to severe pain
  - BD abscess can be so painful that the patient is incapacitated; difficulty in walking or sitting
- **Physical exam**
  - Fever present in one-third of patients
  - Acutely tender swelling at posterior labium majora extending inwards into the base of labium minora
  - Occasionally track anteriorly up L majora (Rouzier, 2005)

---

**BD Abscess Pre-treatment**

- Pregnant, diabetic, or immunocompromised?
  - Yes
    - Admit
  - No
- Large enough to drain?
  - Yes
    - Tolerates manipulation
      - Yes
        - I&D
      - No
        - Conscious sedation in ED or office
  - No
    - Moist heat
      - Abx if induration
      - RTC in 48-72 hours

- Abscess points
- Resolved

Pus: C/S + GC/Ct if STD risks
BD Abscess: I&D Tools and Supplies

- Povidone-iodine solution
- Anesthetic solution (1-2% lidocaine) + insulin needle/syringe
- Word catheter (diameter: #10F Foley catheter)
  - 22-25 gauge needle and 5 mL-syringe, plus water or gel, for inflation of catheter tip
- No. 11 blade scalpel
- Hemostat (for breaking up loculations)
- Saline solution for irrigation
- Collection kits for bacterial culture and GC/Ct NAAT

BD Abscess: Tips for Word Catheter

- Consider topical skin anesthetic with EMLA
- Have assistant retract abscess laterally to select incision site...immediately external to the hymeneal ring
- Inject skin with 1-2 cc. lidocaine
- 5-10 mm. stab with # 11 blade perpendicular to abscess
- Gently lyse loculations with clamp
- Irrigate cavity with saline
- Insert needle into Word port; then test the bulb
- Insert Word catheter; inflate (3-5cc) until snug fit in cavity
- Tuck nipple into vagina
**BD Abscess: Post-Drainage Management**

- Sitz baths and warm compresses for 2-3 days
- Antibiotics not needed routinely after I&D
- If residual cellulitis, SIRS, or immunocompromise, recommended antibiotic regimens include
  
  **Strep:** Cephalosporin (cephalexin or cefixime)
  
  **And for Staph:**
  
  TMP/SMX 1-2 double strength tablets PO BID
  
  or Doxycycline 100 mg PO BID
  
  – If MRSA confirmed, replace doxycycline with TMP/SMX

**Vulvar Abscess: Presentation**

- Painful vulvar mass
  – Described as “pimple” or “boil”
- Vulvar fullness or pressure
- Pain with walking, sitting, or sexual intercourse
- Pain beyond local tenderness, particularly in immunocompromised women, raises suspicion for NF

**Signs**

- Mass, fluctuance, erythema, edema, induration
- Bimanual and rectovaginal exam prn
- Size should be measured and documented
Vulvar Abscess: Microbiology

Typically a polymicrobial infection
• Staphylococcus aureus, streptococcal species, E. coli, and other gram-negative enteric organisms
• Anaerobic bacteria (Peptostreptococcus or B. fragilis)
• GC and Ct are extremely rare
• MRSA is the most common pathogen among women with vulvar abscesses that require I&D
  – Athletes, military recruits, injection drug use, poor hygiene
  – Sharing needles, razors, or other sharp objects

Treatment of Vulvar Abscess

• Abscess <2 cm with mild cellulitis
  – Moist heat: sitz-bath, warm compresses
  – 1st line: TMP-SMX 1-2 DS tabs BID for 5-10 days
  – 2nd line: doxycycline (100 mg BID) or
    • Clindamycin (300-450 mg TID)
  – Follow-up one week later
• Abscess >2 cm or less than 2 cm and present > 1 week
  – I&D, with packing if possible
  – Aerobic c/s for MRSA
  – Follow-up at 2 days and 2 weeks after treatment
Incision & Drainage

- Dome infiltration with local anesthetic
- in A-P axis, incise point with #11 blade
- Send culture
- Break up loculations
- Irrigate
- Pack as needed
- Saline-soaked gauze replaced daily until the defect has closed

Vulvar Abscess: I&D, then Antibiotics

- Extensive or rapidly progressing surrounding cellulitis
- Abscess size $\geq 5$ cm
- Location makes abscess difficult to drain completely
- Infection extends into other anatomic compartments (e.g., abdominal wall or thigh)
- High likelihood of MRSA
- Systemic signs of infection
- Immunocompromised patient
- Recurrent abscess

Chen K, UpToDate. 2016
Treatment of Vulvar Abscess With Cellulitis

• I&D, then antibiotics and serial surveillance
• Antibiotics
  – Staph: TMP/SMX or doxycycline
  PLUS
  – Strept: cephalosporin or clindamycin
• 5-10 days of therapy is recommended
  – Duration of therapy guided by resolution of symptoms

Betsy 17 year old G₀

• While having her LNG IUD placed, Betsy says, “Is this going to take much longer? I really need to go to the bathroom”
• What’s going on here??
Betsy 17 year old G_0

• She recalls after the fact that she had a fainting spell after her HPV immunization
• She had told her PCP about this problem...heart auscultation and an ECG were normal.

Vasovagal Response, Episode Or Attack
AKA: Non-cardiogenic Syncope

• Mechanism
  – Starts with peripheral vasodilation
  – Bradycardia + drop in B/P
• More likely with
  • Pain with cervical manipulation
  • Previous episodes of vaso-vagal fainting
  • Dehydration or NPO

Presyncopal Signs

- Facial pallor (distinct green hue)
- Yawning
- Pupillary dilatation
- Nervousness
- Diaphoresis
- Slurred or confused speech


Presyncopal Symptoms

- Weakness/light-headedness
- Visual blurring/tunnel vision
- Nausea
- Feeling warm or cold
- Sudden need to go to the bathroom
- Tinnitus

Vasovagal Prevention

- Good hydration (electrolyte/ sports drink)
- Eat before placement
- Prophylactically contract muscles if known history


How to Abort a Vasovagal

- Isometric contractions of the extremities
- Intense gripping of the arm, hand, leg and foot muscles
- No need to bring the legs together or change position—just tense the muscles
- These contractions push blood back into the center of the body
- ....and abort the reflex
Missing String...Possibilities

Malpositioned IUD, following perforation or incorrect placement
4. Embedment into the myometrium
5. Translocation into the abdomen or pelvis

Missing String: Office Ultrasound
• No IUD string in canal
• Pregnancy test negative
• Office ultrasound (UTZ)

Desires removal
Extract + guidance
Extracted
Embedded
3D-UTZ or CT with contrast

Desires retention
Leave In Situ
Not found

Present
Absent

Desired removal
KUB
Present
Absent
Expelled

“Formal” UTZ

Present
Absent

Present
Absent

Embedded?

Translocated
Hysteroscopy
Laparoscopy

3D-UTZ or CT with contrast
Missing String: No Office Ultrasound

- No IUD string in canal
- Pregnancy test negative

Desires removal

Attempt extraction

Extracted

Embedded

Op hysteroscopy

Extracted

Not felt

Desires retention

Ultrasound

In Situ

Absent

Present

Translocated

Expelled

KUB

OR

Ultrasound

In Situ

Absent

Present

Translocated

Missing String: Desires Removal

Extraction of IUD in-situ

1. Consent for uterine instrumentation procedure
2. Bimanual exam
3. Probe for strings in cervical canal
4. Apply tenaculum
5. Administer cervical block
6. Choose extraction device
   - Emmett Thread Retriever
   - Patterson alligator forceps
   - Ring IUD: crochet hook or 3-5 mm suction curette
Fulcrum 1 cm from the tip of the device

Opened and closed completely within the uterine cavity

No cervical dilation necessary


---

**Missing String: Desires Removal**

**Extraction of IUD in-situ**

7. Intrauterine exploration for a T-shaped IUD
   - Real-time ultrasound guidance may help, if available
   - Gently open/ close/quarter turn forceps at progressive depths until “purchase” of stem or arm

8. Maneuver hook along anterior, then posterior, uterine wall from fundus to canal

9. If embedment suspected, consider evaluation with 3-D ultrasound or pelvic CT with contrast
   - Extract via operative hysteroscopy or laparoscopy
Why Do CT or 3-D Ultrasound?

Answer: To decide whether to start the extraction with laparoscopy or hysteroscopy!

Missing String: Desires Removal

Additional measures, as indicated

- Pain management
  - Cervical block + oral NSAIDs for pain
  - Conscious sedation
- Cervical dilation
  - Osmotic dilator
  - Rigid dilators
  - Misoprostol *may* facilitate IUD extraction
Identify the Insertion Site

- Inner side of non-dominant upper arm
- Overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus
- 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles

Implant Location After Insertion

- This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus.
- If it is not possible to insert the implant in this location (e.g., in women with thin arms), it should be inserted as far posterior from the sulcus as possible.
Implant Insertion Troubleshooting

- If you pierce the skin, retract and re-insert subdermally
- If the implant protrudes from the insertion site, remove it and perform a new procedure with a new implant
- If the rod is not palpable...
  - Check the applicator (purple tip of the obturator should be visible)
  - Use imaging (x-ray, CT, ultrasound, MRI)
  - Until location is confirmed, counsel to use other method
- Deep implants need to be removed to prevent migration

Implant Removal Tips

- Only attempt removal if you have localized it
  - Identify radiologist who can identify it on u/s
  - Obtain u/s in your clinic
  - Can also obtain etonogestrel level if not radio-opaque
- If you can feel it, you can often remove it
  - Fine mosquito clamps are key
- Identify referral center for deep removals
  - It takes special expertise if below the muscle fascia
Concurrent Workshop

F: Should it Change Your Practice? A Deeper Look at Some of the Past Year’s Most Important Papers

Michael G. Shlipak, MD, MPH

A Year of Unexpected Results from Clinical Trials

1. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease (NEJM)

2. Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer (NEJM)

3. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia (NEJM)
4. Acute Illness Associated With Cannabis Use, by Route of Exposure: An Observational Study (ANNALS)

5. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy (NEJM)

6. Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE): A Randomised, Double-Blind, Placebo-Controlled Trial (The Lancet)

7. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly (NEJM)

8. Effect of Aspirin on Disability-free Survival in the Healthy Elderly (NEJM)

9. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus (NEJM)
Chronic Heart Failure: Effective Diagnosis, Treatment and Monitoring

Michael G. Shlipak, MD, MPH
Scientific Director, Kidney Health Research Collaborative
Professor of Medicine, Epidemiology & Biostatistics
University of California, San Francisco

Associate Chief of Medicine for Research Development
San Francisco VA Medical Center

Outline

• Diagnosis and Staging
• Diastolic Heart Failure
• Systolic Heart Failure Medications
• Devices and End-Stage Heart Failure
Heart Failure Epidemiology

- Only cardiovascular outcome that continues to increase
- Lifetime risk ~20%
- Complicated to manage with multiple other comorbidities
- Treatments improve survival and reduce morbidity substantially.
  - 5 classes of medications improve survival
  - 3 classes of medications improve symptoms
Why is Heart Failure Challenging to Manage?

- Patients are very complicated and often frail
- CHF travels with many other comorbidities:
  - CAD, hypertension, diabetes, CKD
- Polypharmacy
- Diastolic heart failure becoming more common

Question 1: Which of the following establishes a HF diagnosis?

a) EF < 35% on echo
b) BNP > 300 on blood test
c) S3 on exam
d) All of the above
e) None of the above
Heart Failure is a Clinical Diagnosis

- **Essential Symptoms**: dyspnea, fatigue, orthopnea
- **Signs**: rales, edema, JVD, S3
- **Physical exam**: does not distinguish systolic vs. diastolic
- Helpful features include:
  - Chest X-Ray: pulmonary congestion
  - Elevated BNP or Nt-proBNP
  - Echo showing diastolic or systolic dysfunction

Diastolic vs. Systolic Heart Failure

- **Based on the Ejection Fraction**
  - <40%, 40-50%, >50%
- **Diastolic HF (>50%)**:
  - Official term is “Heart Failure with Preserved Ejection Fraction”
  - Abbreviated as HFP EF
- **Systolic HF (<40%)**:
  - Official term is “Heart Failure with Reduced Ejection Fraction”
  - Abbreviated as HFr EF

“Intermediate” – 40-50% (excluded from RCTs)
NYHA Functional Classes

Classes assume a prior diagnosis of heart failure

I. No limitation on ordinary physical activity
II. Slight limitation – ordinary physical activity
III. Marked limitation - < ordinary physical activity
IV. Symptoms or discomfort at rest

Problems with these classes:
• Patients vary across stages, going up and down
• All class 4 at time of hospitalization

AHA (2009) Classification of Heart Failure

A. Risk factors for heart failure- no clear signs/symptoms
B. Asymptomatic LV disease- LVH, diastolic dysfunction, valve disease, low EF
C. Symptomatic heart failure- dyspnea at rest or exertion, fluid retention
D. Advanced heart failure- inotrope requirement, consideration for assist device or transplant
  • Can only progress down the classes
  • Emphasizes prevention over staging

Not HF

Combines stages 1-3
Strategies that apply to all CHF Patients

- Initial ECHO
- Repeat only if major changes
- Salt restriction
- Daily weight monitoring
- Exercise
- Diuretics for symptoms
- Avoid NSAIDS
- Monitor:
  - Volume status
  - Electrolytes, renal function

Outline

- Diagnosis and Staging
- **Diastolic Heart Failure**
- Systolic Heart Failure Medications
- Devices and End-Stage Heart Failure
Question 2: Which of the following improve survival in diastolic heart failure?

a) ACE-I  
b) ARB’s  
c) Beta blockers  
d) Ca-channel blockers  
e) All of the above  
f) None of the above

What is Diastolic Heart Failure?

- “Stiff heart syndrome”- heart cannot relax in diastole to allow the left ventricle to fill
- Causes increased pressure in the left atrium, and pulmonary edema
- Defined by EF, yet actual stroke volume may be same as Systolic HF
- Same signs and symptoms as systolic HF
- Relative prevalence of diastolic HF vs. systolic HF increases with age, and higher in women
Diastolic HF: Good and Bad News

Good news:
• More favorable prognosis than SHF
• Simpler regimen, as diuretics cornerstone of therapy

Bad news:
• Often progresses to SHF
• No therapies improve DHF survival

ACC/AHA Guidelines for DHF Treatment

• BP control (SBP < 130)
• Rate/rhythm control in AF
• Diuretics for pulmonary congestion
• Revascularization and other treatment for coronary ischemia
Outline

- Diagnosis and Staging
- Diastolic Heart Failure
- **Systolic Heart Failure Medications**
- Devices and End-Stage Heart Failure

ACE Inhibitors

- Improve symptoms and reduce hospitalizations
- Decrease mortality risk for all heart failure stages
- Class effect- all ACE inhibitors
- Aim for target dose – 40mg has better outcomes than 5mg (ATLAS trial)
Meta-Analysis of ACE Trials

- 30 RCTs - ACE-I vs. placebo
- Mortality
  - 0.77 (0.67-0.88)
- Death or hospitalization for heart failure
  - 0.65 (0.57-0.74)
- Specific ACE-I’s with benefits in RCT’s:
  - Benkapril - Enalapril - Ramipril
  - Captopril - Lisinopril

Kidney Function and ACE Inhibitors in Heart Failure

- Clinical trials show benefit if estimated GFR > 30
- No evidence for lower GFR levels
- Expect the creatinine to rise at least 30%
- Even creatinine doubling is OK - typically returns near baseline
- Worry about K increase (keep < 5.5); balance the K with diuretic dose.
- Continue ACE-Is as eGFR declines unless cannot control K.

Shlipak MG, Ann Intern Med 2003
**ARBs in Systolic Heart Failure**

- Generally equivalent to ACE inhibitors
- Use for patients with cough on ACE inhibitors
- Combination of ACE and ARB?
  - Decreases hospitalization risk; increases adverse effect risk (increased K)
  - No survival difference
  - Generally, not recommended, as safety probably lower in actual practice


**Question 3: What is an “ARNI”?**

- A. Novel heart failure agent that slows down the SA node to allow greater ventricular filling
- B. New class of heart failure drugs that prevents arrhythmias so patients will not require an ICD
- C. A combination of an Angiotensin Receptor Blocker with a medication that blocks neprilysin
- D. A novel beta-blocker that has the ability to increase ejection fraction
- E. All of the above
PARADIGM-HF Trial: Angiotensin-Receptor blocker/Neprilysin Inhibitor (ARNI) vs. Enalapril

PARADIGM-HF Trial
- N=8,442
- Class 2-4 HF symptoms
- EF< 40%
- The new drug:
  - LCZ696
  - Valsartan/Sacubitril
  - Entresto
  - 2015 FDA approval
- Sacubitril- blocks Neprilysin →
- ↓ vasoconstriction, ↓ Na retention, ↓ remodeling
- Prior ARNI- Omipatrilat (caused ↓ BP, angioedema, and cognitive dysfunction)
PARADIGM-HF Trial

- **Inclusion Criteria:**
  - EF < 40%
  - BNP > 150
  - Prior ACE/ARBs

- **Exclusion Criteria:**
  - SBP < 95
  - eGFR < 30
  - K > 5.2
  - ACE/ARB angioedema

### Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Mean Age</td>
<td>64</td>
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<tr>
<td>% Female</td>
<td>22%</td>
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<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>66%</td>
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<tr>
<td>Black</td>
<td>5%</td>
</tr>
<tr>
<td>Asian</td>
<td>18%</td>
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<tr>
<td>Other</td>
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<tr>
<td>Mean BP</td>
<td>122/72</td>
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<tr>
<td>Mean Creatinine</td>
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<tr>
<td>% eGFR&lt;60</td>
<td>36%</td>
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<tr>
<td>Class 2</td>
<td>70%</td>
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<tr>
<td>Class 3</td>
<td>24%</td>
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PARADIGM-HF Trial

Baseline Characteristics of Patients (continued)

<table>
<thead>
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<th>Medications</th>
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<tbody>
<tr>
<td>ACE/ARB</td>
<td>100%</td>
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<td>BB</td>
<td>93%</td>
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<tr>
<td>Diuretics</td>
<td>80%</td>
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<td>Aldo-Antagonist</td>
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<td>Digitalis</td>
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<thead>
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<th>Devices</th>
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<td>ICD</td>
<td>15%</td>
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<tr>
<td>CRT</td>
<td>7%</td>
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</table>

PARADIGM-HF Trial

Enrollment in 3 Phases

1.) Enalopril 10mg 2x/day: 2 weeks (N= 10,513)  
   - 10% drop out (5.6% - adverse effects)

2.) ARNI: 4 weeks (N=9,419)  
   - 100 mg and 200 mg  
   - 10% drop out (5.8% - adverse effect)

3.) RCT: Enalopril (10 mg 2x/day) vs. ARNI (200 mg 2x/day) (N=8,442)  
   - trial stopped early  
   - median follow-up 27 months
### PARADIGM Trial

**Primary and Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome – (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV Death or HF Hospitalization</td>
<td>21.8%</td>
<td>26.5%</td>
<td>0.80 (0.73-0.87)</td>
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<tr>
<td>CV Death</td>
<td>13.3%</td>
<td>16.5%</td>
<td>0.80 (0.71-0.89)</td>
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<tr>
<td>HF Hospitalization</td>
<td>12.8%</td>
<td>15.6%</td>
<td>0.79 (0.71-0.89)</td>
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<tr>
<td>Secondary outcomes – (%)</td>
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<tr>
<td>Death</td>
<td>17.0%</td>
<td>19.8%</td>
<td>0.84 (0.76-0.93)</td>
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</table>

### PARADIGM Trial

**Adverse Events during Randomized Treatment**

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<tr>
<th>Event</th>
<th>LCZ696 (N=4,187)</th>
<th>Enalapril (N=4,212)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Hypotension</td>
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<tr>
<td>Symptomatic</td>
<td>14.0%</td>
<td>9.2%</td>
<td>&lt;0.001</td>
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<tr>
<td>Elevated serum creatinine ≥ 2.5 mg/dl</td>
<td>3.3%</td>
<td>4.5%</td>
<td>0.007</td>
</tr>
<tr>
<td>Elevated serum potassium &gt; 6.0 mmol/liter</td>
<td>4.3%</td>
<td>5.6%</td>
<td>0.007</td>
</tr>
<tr>
<td>Cough</td>
<td>11.3%</td>
<td>14.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0.5%</td>
<td>0.2%</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Controversies around Entresto

- Cost- $4,560/year
  - Pay for performance models?
- Single trial
  - Only 5% Blacks
  - Low % with devices
  - Run in period required tolerance to the drug
- Potential “off target” effects?
  - Hypotension
  - Cognitive decline a concern (with Omipatrilat)

Recommendations around Entresto

**Recommendations**
1.) Class 1 agent for systolic HF
2.) For use in patients who are stable on maximum ACE or ARB
3.) Never use in combination with ACE or ARB (wait 3 days off ACE/ARB)
**Beta Blockers in Systolic Heart Failure**

- Beta blockers improve symptoms and increase ejection fraction by 5-10%
- Beta blockers decrease mortality in systolic heart failure, from both pump failure and arrhythmic causes
- Unlike ACE inhibitors, not a class effect
- Metoprolol, Carvedilol, Bisoprolol

**Heart Failure Survival**

![Graph showing risk reduction and confidence intervals for beta blockers in heart failure].

*Figure 3: β-Blocker mortality trials: all-cause mortality results. CIBIS II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.*

Ramani G et al., Mayo Clin Proc 2010
Challenge of Titrating Beta Blockers in Heart Failure Patients

- BB’s require subtle dose increases at 2 week intervals
- Can take up to 6 visits to reach target
- Hypo-tension is not a contra-indication unless symptomatic (even if SBP<90)
- Carvedilol may be more difficult to titrate dose up.
- Benefit greatest at maximum dose
- Unfortunately, many patients left at the low starting dose

Other Therapies in Systolic Heart Failure

- Diuretics
- Aldosterone Antagonists- spironolactone, eplerenone
- Hydralazine/Nitrates
- Invabradine
Diuretics

- Rapid relief of dyspnea and fluid retention
- Aim for lowest dose that reaches “dry weight”
- Therapeutic goals:
  - Improved dyspnea and orthopnea
  - Minimal pre-tibial edema
- Patients can manage the dose and schedule

Diuretic Refractory Patients

- Periodic thiazide (metolazone)
  - e.g. 3x/week doses
  - watch for hypo-Na+, hypo-K+
- Change the loop diuretic- furosemide (Lasix), bumetanide (Bumex), Torsemide (Demadex)
- Long-acting nitrates also useful for symptoms
- Occasional IV diuretics may be required- intestinal edema can block po absorption
Aldosterone Antagonists
(spironolactone, eplerenone)

- Improve survival and reduce hospitalization-RALES trial
- Only studied in NYHA class 3-4 heart failure patients on ACE inhibitors
- K allowed up to 5.6; very few hyper-K complications
- 1/3 on beta blockers

Pitt B. et al., NEJM 1999

Enormous Rise in Spironolactone Use

Juurlink DN et al., NEJM 2004
Epidemic of Hyper-K Followed

What Happened?

- It’s in the fine print…
- RALES methods- inclusion if patients Cr < 2.5
- 2005 AHA Guidelines- spironolactone recommended in NYHA III heart failure if Cr < 2.5
- RALES table 1- actual Cr levels 1.2 ± 0.3
  - ~80% had Cr ≤ 1.5
  - ~ all had Cr < 2.0
  - average furosemide dose of 80mg
Case Details of Hyper-K on Spironolactone

- Case reviews of critical or fatal hyper-K (≥ 6.5) Schepkers et al., Am J Med 2001
- Mean Cr of 2.1; all on ACE-I also
- Often in setting of other illness- decreased oral intake
- Lessons learned:
  - Caution in using spironolactone if eGFR < 45
  - Stop spironolactone in acute illness

Guideline Recommendations on Aldosterone Antagonists

- AHA HF guidelines (2005, 2009, 2013) have vasillated on aldosterone antagonists
  AHA Class I:
  - Recommended for HF patients EF< 35%
  - eGFR> 30; K < 5.0
  AHA Class III (harmful):
  - eGFR< 30, K > 5.0
  My recommendation: Use extreme caution if eGFR 30-45
  - QOD dosing: cutting dose by ½
  - Advise patients to stop using when PO intake is reduced or acutely ill
Hydralazine and Nitrates


- 1,040 African American patients
- Hydralazine vs. Placebo
- Trial halted early
- HR = 0.57, p = 0.01

Hydralazine/Nitrates

- Recommended (Class I) for “self-described” African Americans
  - Reduced EF
  - Class III/IV symptoms
  - Already treated with ACE, BB
- Consider (Class 2A) in patients who cannot tolerate ACE/ARB, such as in advanced CKD
Ivabradine (Corlanor)

**SHIFT Trial**

- New class of HF drug
- Slows HR at SA node (If current)
- Patients EF<35%, HR>70, on BB
- Results:
  - ↓ HF Hospitalization: 16% vs 21% (0.74; 0.66-0.8)
  - No difference in mortality risk
- AHA recommendation: class 2A for patients with HF and EF<35%
- Opinion: no clear role for this drug in most patients

_Swedberg, Lancet 2010_

Outline

- Diagnosis and Staging
- Diastolic Heart Failure
- Systolic Heart Failure Medications
- Devices and End-Stage Heart Failure
**Rationale for Implantable Cardiac Defibrillators (ICDs) in CHF**

- Ventricular arrhythmia - common cause of heart failure death
- ICDs can reverse VT/VF and save the patient
- VT/VF risk is highest in end-stage CHF patients; but those patients unlikely to survive to gain benefit
- Challenge for selecting ambulatory patients for ICDs:
  - VT/VF risk high enough to benefit
  - CHF moderate, so patient might live a few years

**ICD’s in Secondary Prevention**

- Studied in Systolic HF patients
- Patients who survived prior sudden death or unstable VT event
- ICD’s clearly improve survival
- Must be consistent with goals of care for patient/family – critical role for the PCP
ICDs in Primary Prevention

- Risk/benefit tradeoff
- Recommended for patients with EF < 35% AND:
  - moderate HF symptoms on appropriate treatment
  - expectation of survival > 1 year
  - Not for class 4 HF - prognosis too poor to benefit, unless as a bridge to transplant
- Prior MI patients appear to have higher SCD risk, among those with Systolic HF

Rationale for CRT
(Cardiac Resynchronization Therapy)

- **Cardiac dys-synchrony:**
  - Concern in patients with EF< 35%
  - RV and LV may not be in harmony
  - Suspect dyssynchrony in patients with persistent symptoms despite ideal treatment
- **Causes:** decrease ventricle filling, decrease EF, increase MR
- **CRT:** activates LV/RV together with bi-ventricular pacer
- **Meta-analysis:**
  - decrease in mortality by 25%
  - detectable after 3 months  
  
  McAlister FA, JACC 2004
Ideal Candidates for CRT

- EF < 35% and persistent symptoms
- 3 additional ECG criteria:
  - Sinus rhythm
  - LBBB
  - QRS > 150mg
- **Class I**: all 3 ECG criteria
- **Class 2A**: 2 of 3 ECG criteria
- **Class 2B**: 1 of 3 ECG criteria

End-Stage Heart Failure

**European Definition of Class D/Advanced HF**
- Severe symptoms at rest or with minimal exertion
- Hospitalized in last 6 months
- Treatment already optimized
- Poor functional status

**Clinical correlates of Advanced HF**
- Weight loss
- Worsening kidney function
- SBP<90
- Intolerance to ACE and/or BB
- Na<133
- Increasing diuretic requirement
- Frequent ICD shocks
Additional Support for End-Stage Heart Failure Patients

Consider:

- Specialized strategies (HF specialist):
  - Mechanical circulatory support
  - Inotrope infusions
  - Transplant or surgery referral

- Hospice/End-of-Life Care (Palliative care)
  - Comfort care
  - Turn off the ICD

Thank you!
MANAGING HYPERTENSION IN 2019
How Do We Work With Conflicting Data and Conflicting Guidelines?

Robert B. Baron, MD MS
Professor and Associate Dean
UCSF School of Medicine
baron@medicine.ucsf.edu

Disclosure

No relevant financial relationships
69 yo woman, annual visit. BP 148/88. No diabetes, no CAD/CVD, kidney normal. 10 year CV risk 10%. Otherwise well. Follows all lifestyle recommendations. The next best step is:

1) Start HCTZ
2) Start ACEI or ARB
3) Start calcium channel blocker
4) Start beta blocker
5) Continue to observe

69 yo woman, annual visit. BP 148/88. No diabetes, no CAD/CVD, kidney normal. 10 year CV risk 10%. Otherwise well. Follows all lifestyle recommendations. Your treatment goal is:

1) <150 mm Hg
2) <140 mm Hg
3) <130 mm Hg
How Should We Measure Blood Pressure?

Office measurement: most common, used in clinical trials

Home BP measurement: less intensive drug Rx & less BP control. Identifies “white-coat” HTN

Ambulatory monitor: best correlation with CVD

Baron RB, JAMA Int Med. 2018

Accurate Office BP Measurement

1) Patient seated for 5 minutes in chair
2) Back supported and feet on ground
3) No caffeine, exercise, smoking for 30 minutes
4) No talking by patient or observer
5) Removal of clothing under cuff
6) Support arm horizontally at level of atrium
7) Correct cuff size
8) Repeat measurements with results averaged

Whelton PK, JACC, 2017
Accurate Office BP Measurement

- Failure to adhere may lead to dramatic increase in BP

- For example:
  - Recent study in 20 clinics
  - All BP ≥ 140/90 repeated by MA
  - 36% had normal second measurement

Einstadter D, JAMA Inter Med, 2018

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Accurate Office BP Measurement

- Which value should you record?

- Guidelines: average multiple measurements
- HEDIS (and other quality measures): OK to use lowest measurement
Accurate Office BP Measurement

- What about “research grade” measurement?
- Systolic BP Intervention Trial (SPRINT)
  - 5 minutes rest
  - 3 automated measurements
  - No human in room
- Research grade was 12.7 mm Hg lower than routine office measurement

USPSTF: Screening for HTN 2015

- Begin at age 18
- Measure carefully
- Obtain measurements outside of the clinical setting before starting treatment
- 2016 NICE Guidelines (United Kingdom) concur
Accurate Home BP Measurement

- Not well standardized
- Not fully evidence-based
- Correct home monitoring requires
  - Patient training
    - Same principles as office measurement
  - Correct equipment
  - Correct timing
    - AM before meds and before dinner

Accurate Home BP Measurement

- Home measurements lower, but relationship not uniformly predictable
- Correlation with ambulatory monitoring about 60-70%
- Clinical trials of home monitoring alone to improve BP control have shown little impact at 6-12 months
Ambulatory BP Monitoring (ABPM)

- Best approach to out-of-office measurement
- Several times per hour during normal daily (and nighttime) activities
- Lower than office, but relationship unsettled
- ABPM better predicts CV risk than office measurement

Piper MA, Ann Int Med, 2015

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Ambulatory BP Monitoring (ABPM)

- Most effective at detecting white coat HTN
- Monitor drug treatment
- Detect occasional patient with normal office BP but elevated out-of-office BP (“masked HTN”)

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**Summary BP Measurement 2018**

- Clear office strategy: training, work flow, physical settings. Consider “research grade” approach
- Repeat measurements (MA or MD)
- Decide which measure to record (averaged or lowest)
- Home measurements for some patients; use best practices
- Use ambulatory monitoring more, but not in every patient

**Lifestyle Modifications for BP Control**

- Weight loss if overweight: 5-20 mm Hg/10-kg weight loss
- Limit alcohol to ≤ 1 oz/day: 2-4 mm Hg
- Reduce sodium intake to ≤100 meq/d (2.4 g Na): 2-8 mm Hg in SBP
- DASH Diet: 6 mm alone; 14 mm plus Na
- Physical activity 30 min/day: 4-9 mm Hg
- Habitual caffeine consumption not associated with risk of HTN
Managing Hypertension in 2019

Salt in the US Diet

80% in processed or prepared foods

Sources: Mattes et al.

NHLBI Panel on BP (aka Joint National Commission 8)

Three questions:
1) Does Rx at specific BP thresholds improve outcomes?
2) Does Rx to a specific BP goal improve outcomes?
3) Do various meds differ on outcomes?

Nine recommendations
Recommendations for Management of Hypertension

Recommendation 1
≥60 years:

- Lower BP at SBP ≥150 mm Hg or DBP ≥90 mm Hg
- Treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg.

Strong Recommendation – Grade A (but not unanimous)

Evidence from 6 studies of patients over age 60, treated to goal ≤150/90: HYVET, Syst-Eur, SHEP, JATOS, VALISH, CARDIO-SIS

Some evidence (lower quality) comparing ≤160 to ≤140 and ≤150 to ≤140 showing no additional benefit
Key Points of JNC 8

- ≥60 yo: goal ≤150
- Others <140/<90 (including DM, CKD, race/ethnicity)
- Non blacks: thiazide, CCB, ACEI, ARB
- Blacks: thiazide, CCB
- CKD: ACEI or ARB

SPRINT

- 9,361 men and women 50 and over (30% over age 75)
- SBP > 130 mm Hg
- Increased CV risk (but no DM)
- Design <120 mm Hg vs <140 mm Hg
  - 2.7 meds vs. 1.8 meds
- Actual 121.4 mm Hg vs 136.2

SPRINT, NEJM, 2015
**Intensive BP Control in Type 2 DM: ACCORD**

- RCT of 4733 patients with type 2 DM
- Compare BP less than 120 mm Hg vs 140

<table>
<thead>
<tr>
<th></th>
<th>120</th>
<th>140</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>119</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>CV events plus death</td>
<td>1.87%</td>
<td>2.09%</td>
<td>.20</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.28%</td>
<td>1.19%</td>
<td>.55</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.32%</td>
<td>0.53%</td>
<td>.01</td>
</tr>
<tr>
<td>Adverse events</td>
<td>3.3%</td>
<td>1.3%</td>
<td>.001</td>
</tr>
</tbody>
</table>

In type 2 DM: treating to 120 mm Hg did not reduce the rate of composite fatal and non-fatal CV events

**SPRINT: Results**

- **Composite outcome**
  - 243 events (1.65% per year) vs 319 (2.19% per year)
  - HR 0.75 (0.64 – 0.89)

- **All cause mortality**
  - 155 (1.03% per year) vs. 210 (1.40% per year)
  - HR 0.73 (0.60 – 0.90)
**SPRINT: Adverse Events**

- Hypotension: HR = 1.67 (p = 0.001)
- Syncope: HR 1.33 (p = 0.05)
- Electrolyte abnormality: HR 1.35 (p = 0.02)
- Acute kidney injury: HR 1.66 (p < .001)

**NNT and NNH from SPRINT**

<table>
<thead>
<tr>
<th>Over 3.26 years of trial...</th>
<th>NNT</th>
<th>NNH</th>
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</thead>
<tbody>
<tr>
<td>Primary aggregate outcome</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>Death from any Cause</td>
<td>90</td>
<td>-</td>
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<tr>
<td>Death from CVD</td>
<td>172</td>
<td>-</td>
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<tr>
<td>Serious Adverse Event</td>
<td>-</td>
<td>45</td>
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<tr>
<td>Hypotension</td>
<td>-</td>
<td>72</td>
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<tr>
<td>Syncope</td>
<td>-</td>
<td>93</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>-</td>
<td>56</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>-</td>
<td>97</td>
</tr>
</tbody>
</table>
SPRINT Reflections

- SPRINT showed that SBP <120 had better CVD/mortality benefit than SBP <140 (NNT 61 over 3 years)...

- But, notable adverse effects with a NNH 45 over 3 years.

- Generalizability: would only apply 1/6 of current patients treated for HTN

SPRINT Reflections

- No DM, no stroke, no frail elderly, > age 50

- ASCVD risk: ≥15% ten year risk to enter (actual risk ≥20%)

- Free care, frequent visits, research grade BP measurement
Managing Hypertension in 2019

1000 people treated 3.2 years to an SBP goal <120 compared to <140

16 Benefit

22 Harmed

SPRINT Reflections

“This strategy would represent a big shift in the approach to screening and treatment, and in my view, the findings need replication before intensive treatment can be pushed as the standard of care.”

Harlan Krumholz, MD
ACP/AAFP Guidelines

- Over age 60:
  - Goal <150 mm Hg

- For patients over age 60 with stroke/TIA, high CV risk:
  - Goal < 140 mm Hg

ACC/AHA 2017 Guidelines

- Normal <120 (and DBP <80)

- Elevated 120 – 129 (and DBP <80)

- Hypertension
  - Stage 1 130 -139 (or DBP 80-89)
  - Stage 2 ≥140 (or DBP ≥90)
ACC/AHA 2017 Guidelines

- Secondary Prevention <130 and <80
- Primary Prevention <130 and <80 (ASCVD Risk ≥10%)
- Primary Prevention <140 and <90 (ASCVD Risk <10%)

JACC, November 2017

Meta-Analysis of BP-Lowering, Mortality and CV Disease

- RCTs of BP meds vs. placebo
- 74 trials; 306,273 patients
- 40% women, mean age 63.6 years

Brunstrom M, JAMA Int Med, 2018
Meta-Analysis of BP-Lowering, Mortality and CV Disease

- If BP >160 mm Hg
  - Death 0.93*
  - CVD events 0.78*

- If BP 140 - 159 mm Hg
  - Death 0.87*
  - CVD events 0.88*

*Statistically significant

Brunstrom M, JAMA Int Med, 2018

Meta-Analysis of BP-Lowering, Mortality and CV Disease

- If BP <140 mm Hg
  - Death 0.98 (NS)
  - CVD events 0.97 (NS)

- If prior CHD and mean BP 138 mm Hg
  - Death 0.98 (NS)
  - CVD events 0.90*

Brunstrom M, JAMA Int Med, 2018
AAFP and ACP Both Decide Not to Endorse AHA/ACC Guidelines

- JNC 8 upheld scientific rigor but AHA not based on systematic evidence review
- Mostly based on SPRINT
- Would lead to 46% of population categorized as HTN (vs 32%)

Antihypertensive Treatment in Low Risk Patients

- British cohort study, 38K patients, 5.8 years, ages 18–74, 56% women
- SBP 140–159 mm Hg and 90 – 99 mm Hg: untreated vs treated
- No difference in mortality, CVD
- Treatment associated with increased
  - Hypotension (↑69%, NNH 41)
  - Syncope (↑28%, NNH 35)
  - Electrolyte (↑72% NNH111)
  - AKI (↑37%, NNH 91)

Sheppard J, JAMA Int Med, 2018 (October)
69 yo woman, annual visit. 
BP 148/88. No diabetes, no CAD/CVD, kidney normal. 10 year CV risk 10%. Otherwise well. 
Follows all lifestyle recommendations. The next best step is:

1) Start HCTZ 
2) Start ACEI or ARB 
3) Start calcium channel blocker 
4) Start beta blocker 
5) Continue to observe (my preference)

69 yo woman, annual visit. 
BP 148/88. No diabetes, no CAD/CVD, kidney normal. 10 year CV risk 10%. Otherwise well. 
Follows all lifestyle recommendations. Your treatment goal is:

1) <150 mm Hg 
2) <140 mm Hg 
3) <130 mm Hg
Managing Hypertension in 2019

Robert Baron MD, MS

Final Thoughts

- Rethink the way BP is measured in your office
- Take BP accurately yourself and record it (the lowest of the measurements)
- Use home monitoring with greater rigor
- Consider ambulatory BP monitoring before making major treatment decisions
- Use ASCVD risk for HTN decisions, too. For 1º prevention: 10% or 15% or 20%?

Final Thoughts

- Use goal <140/90 for most patients
- Use <150/90 for many/most older patient
- Use <130/80 for some high risk patients (mostly CVD secondary prevention)
Final Thoughts

- Use shared decision-making

- Use team approaches and build trust with patients and families (and specialty colleagues)

- Emphasize primary prevention of high blood pressure
Screening and Diagnosing Dementia in Primary Care

Leah Karliner, MD, MAS
Division of General Internal Medicine
University of California, San Francisco

Why is dementia important?

• Alzheimer Disease is the 6th leading cause of death in the U.S.
• 5.4 million individuals affected
• 1 in 8 Americans aged 65 and older is affected by Alzheimer’s Disease
• In 2013, Americans provided 17.7 billion hours of unpaid care to people with AD and other dementias
• In 2014, AD cost Medicare and Medicaid ~$150 billion
What is dementia?

• An acquired, progressive, persistent impairment in cognition or behavior
• Involves 1 or more cognitive domains
• Sufficient to cause a decline from a previous level of functioning
• Dementia is no longer a diagnosis of exclusion

Risk and protective factors

Risk Factors
• Increased age
• Vascular disease
• Genetics (ie ApoE4)
• Head injury
• Lower education
• Chronic inflammation

Protective Factors
• Physical exercise
• Social engagement
• Mental activity
• Education
How do you currently screen patients for cognitive impairment or dementia?

A. I rarely or never screen my patients
B. I am inconsistent about how/if I screen patients
C. I screen all of my older patients regardless of symptoms or risk factors
D. I screen all of my older patients with known risk factors only
E. I only screen patients with symptoms or whose companion/caregiver brings up cognitive concerns

USPSTF Guideline

• Last reviewed in 2014; current update in progress
• USPSTF distinguishes between screening and early detection
  – “I” or insufficient evidence for formal screening instruments in community-dwelling adults in the general primary care population who are older than age 65 years and have no signs or symptoms of cognitive impairment
  – Early detection and diagnosis of dementia through the assessment of patient-, family-, or physician-recognized signs and symptoms, some of which may be subtle, are not considered screening
    • clinicians should remain alert to early signs or symptoms of cognitive impairment (for example, problems with memory or language) and evaluate as appropriate
Barriers to dementia screening and early detection in primary care

• Concern re: offending patient
• Unsure of who to screen
• Time it takes away from other medical issues during visit
• Not knowing what to do with the information
• Sense of futility due to limited treatments
• Challenges of screening / diagnostic testing; e.g., lack of familiarity with screening tools, time, language barriers

Rationale for screening in primary care

• Screening $\rightarrow$ identification of cognitive impairment
• Identification allows
  – Treatment of reversible causes of cognitive impairment
  – Treatment of conditions exacerbating cognition in dementia
  – Treatment that can mitigate dementia-related symptoms
  – PCP ability to contextualize screening for and treatment of other diseases and provide anticipatory guidance
  – Referral to community-based resources for both patients and caregivers
    • Educational, support, and skill-building services
Where to begin?

KAER Model – Gerontological Society of America 2017

Kickstart the conversation
Assess for cognitive impairment
Evaluate for dementias
Refer for community resources


KAER Step 1: Kickstart the Conversation

• Discuss brain health
  – Raise the issue; e.g., ‘brain ages like other parts of our bodies & is important for your overall health’
  – Opens the door for patients to express any concerns

• Observe for signs and symptoms of cognitive impairment
  – “poor historian”
  – No-shows for appointments or comes at the wrong time or on the wrong day
  – Repeatedly and apparently unintentionally fails to follow instructions; e.g., changing medication
  – Defers to family member to answer questions directed to the patient

• Listen for older adult and family concerns about cognition
Case

• 80 yo retired chemist who is highly functional and living independently with his wife mentions toward the end of a visit that he sometimes has trouble finding the right word, and then says ‘but of course everyone has that problem, right?’

What do you do next?

A. Reassure patient that yes everyone has that problem & it is completely normal
B. Explore further, asking about other signs/symptoms of cognitive impairment
C. Do a formal cognitive screen in the office
D. Send for formal neuro-cognitive testing
KAER Step 2: Assess for Cognitive Impairment

- Normal brain aging can affect word-retrieval
- It can also be a sign of mild cognitive impairment, or – if affecting function – early dementia
- The patient’s concern merits further assessment by history
- A formal cognitive screen in the office may be reassuring or highlight cognitive deficits in specific domains

KAER Step 2: Assess for Cognitive Impairment

- For a review of how to do this in context of Medicare Annual Wellness Visit: Cordell et al. Alzheimer’s & Dementia 9 (2013)
  - Review functional deficits (e.g. managing medications, schedule, money)
  - Make your own assessment during the visit
  - Elicit patient and caregiver (if present) concerns
  If from above, signs or symptoms of cognitive impairment, then do formal cognitive screen

- Many screening tools available all with advantages and disadvantages
<table>
<thead>
<tr>
<th>Tool</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Cog</td>
<td>Developed for and validated in primary care and with multiple languages and cultural groups</td>
<td>Use of different word lists may affect failure rates</td>
</tr>
<tr>
<td></td>
<td>Little or no education/language/cultural bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Short administration time</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>Most widely used and studied worldwide</td>
<td>Education/age/language/cultural bias</td>
</tr>
<tr>
<td></td>
<td>Required for some drug insurance coverage</td>
<td>Ceiling effect (highly educated impaired patients pass)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proprietary – unless used from memory needs to be purchased</td>
</tr>
<tr>
<td>MoCA</td>
<td>Designed to test for mild cognitive impairment</td>
<td>Lacks studies in primary care</td>
</tr>
<tr>
<td></td>
<td>Multiple languages accessible on website</td>
<td>Education bias (≤12 years)</td>
</tr>
<tr>
<td></td>
<td>Tests many separate domains</td>
<td>Admin time ≥ 10 min</td>
</tr>
</tbody>
</table>

Case

- Because it was designed to catch mild cognitive impairment, you decide to screen your patient (80 year old chemist) for dementia using the MoCA, so you schedule him for a follow-up visit for just this purpose.

- He scores 25/30 – scores normally except for memory
  - He recalls 0/5 words on delayed recall
  - With category prompting he recalls 4/5
• This positive screening test merits further diagnostic evaluation

• Many patients (~50%) with cognitive impairment never get a diagnostic evaluation for dementia
  – PCP may not do evaluation
  – Family may not want evaluation
  – Patient may not want / follow-through on evaluation

Boustani et al 2005
Fowler et al 2015
Kotagal et al, 2014
McCarten et al, 2012

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Phenotyping dementias is important for appropriate treatment and anticipatory guidance

- Lewy Body Disease
- Frontotemporal dementia
- Progressive supranuclear palsy
- Corticobasal degeneration
- Multiple system atrophy
- Amyotrophic lateral sclerosis
- Triplet repeat disease (ie Huntington's Disease)
- Paraneoplastic disorders
- Hashimoto's encephalopathy
- CNS lymphoma
- Rapidly progressive dementias (ie Creutzfeld-Jakob disease)

Adapted from Plassman et al., 2007
Evaluate for Dementia

In the context of a medical history with patient and informant assessing for
--onset, course and nature of memory & other cognitive impairments
--associated behavioral, medical, psychological issues
--recent illness, falls & head injury, medications, OTC/herbals, substance use
--vision and hearing problems, depression
1. determine if there is a non-dementia condition causing cognitive impairment
2. Determine if patient meets diagnostic criteria for neuro-cognitive disorder
3. identify the cause of neurocognitive impairment

Evaluate for Dementia

1. determine if there is a non-dementia condition causing cognitive impairment

- Medication/substance evaluation
  - Opioids, TCAs, benzos, non-benzo hypnotics, muscle relaxants, antihistamines, anti-epileptics
  - Substances: alcohol, drugs

- Sensory & Mood assessment: Vision, hearing, depression

- Labs: exclude underlying infection, uremia, liver and thyroid disease; check B-12, folate, calcium, fasting glucose, HIV

- Neuro-imaging: MRI (or non-con CT) to exclude tumors, subdural hematomas, hydrocephalus
Evaluate for Dementia

2. **Determine if patient meets diagnostic criteria for neuro-cognitive disorder**

- **DSM-V** (American Psychiatric Association, 2013): Impairment(s)
  - in 1 or more of 6 cognitive domains:
    - Complex attention, executive function, learning and memory, language, perceptual-motor, social cognition
  - must be a decline from previous level of functioning
  - Interfere(s) with independent functioning
  - do not occur solely in course of delirium

Evaluate for Dementia

2. **Determine if patient meets diagnostic criteria for neuro-cognitive disorder**

- **Functional Assessment**
  - **Activities of Daily Living:**
    - bathing, dressing, toileting, transferring, continence and feeding
  - **Instrumental Activities of Daily Living:**
    - using the telephone, shopping, food prep, housekeeping, laundry, transportation, ability to manage medications and finances

- Cognitive impairment interference with function – key distinguishing factor between mild cognitive impairment (MCI) and Dementia
Evaluate for Dementia

3. identify the cause of neurocognitive impairment

- **Neurologic exam**
  - Gait disturbance (Parkinsonism, FTD, NPH, stroke)
  - Lateralizing signs on cranial nerve exam or indolent HA – consider space-occupying lesion
  - Focal weakness (vascular, Parkinson’s)
  - Bradykinesia, rigidity or tremor (Parkinsonism)
  - Assess for neuropathy due to toxins or vitamin deficiencies

- **Neuropsychological Testing** helpful for
  - Very early stage dementia
  - Evaluating atypical presentations
  - Comprehensive, objective info re: which cognitive functions are affected

Case Study: A 76 yo Chinese-American woman with forgetfulness

- **CC:** “My memory is not as good as it used to be, but overall it’s fine.”
- **PMH:** Hypertension, hyperlipidemia
- **Neurological exam:**
  - Socially intact but with a paucity of spontaneous speech
  - Gait instability
- **MoCA:** 21/30 missing points for orientation, memory, copy of cubes

- **Depression?**
- **Insight?**
- **Fall risk**
- **Executive, memory and visuospatial**
What is the Diagnosis?

A. Normal aging
B. Alzheimer’s Disease (AD)
C. Vascular dementia (VaD)
D. Alzheimer’s Disease + Vascular dementia

Answer: It depends on the MRI
For vascular dementia, look on T2 or FLAIR sequences for...

Periventricular white matter (PVWM) changes (FLAIR image)
Lacunar infarcts
In AD, look for hippocampal atrophy

- Normal hippocampus
- Atrophy of hippocampus

**Alzheimer’s Disease (AD)**

- 1st symptom: Difficulty **encoding** new memories (due to hippocampal atrophy)
- Will spread to include other cognitive domains
- Usually social graces and motor functions are spared until late in disease
AD symptoms mirror its spread through connected neuronal circuits

Early  Middle  Late

• 1st symptom: Difficulty retrieving memories (sub-cortical pattern of memory impairment)
• Stepwise progression
• Oftentimes accompanied by executive dysfunction, parkinsonism, psychiatric disturbance (paranoia, hallucinations)
• Vascular dementia is distinct from stroke
Diagnosis of vascular dementia

- Can be difficult
  - Symptoms and impairments similar to AD
  - Research shows that physicians don’t always agree
- Presence of peri-ventricular white matter (PVWM) changes on MRI does not rule out AD
- Absence of PVWM changes makes AD more likely
- Problems with balance and walking are more common in early vascular dementia
- Differs from stroke in non-acute onset and progressive impairment without recovery over time

Current Treatment of AD and VaD are similar

- Acetylcholinesterase inhibitor (ie donepezil)
- SSRI for depression and/or irritability
- Exercise regimen +/- physical therapy
- Home safety evaluation to prevent falls, accidents
- Planning for the future
- Caregiver support
Refer to Resources in the Community

• Area Agencies on Aging
  – Network of ~620 organizations nationwide
  – Serve elderly populations of their local areas
  – Receive federal funding under Older American Act
  – Provide services: nutrition, caregiver support, information & referral,
    long term care ombudsmen, insurance counseling, transportation
  – No hands on care, no Medicaid planning, no Veterans benefits planning

• Community Resource Finder
  https://www.communityresourcefinder.org/
  – Patients/families can identify needs and find specific resources

• Alzheimer’s Association https://www.alz.org/
  – Focus on Alzheimer’s Disease care, support, and research
  – Website has patient and caregiver centered resources
    • Diagnosis, treatment, research
    • Help & Support, including finding local chapters
Refer to Clinical Trials

• NIA’s ADEAR Center website, Find Alzheimer’s Disease and Related Clinical Trials [https://www.nia.nih.gov/alzheimers/clinical-trials](https://www.nia.nih.gov/alzheimers/clinical-trials)
  – free online resource that allows users to search for relevant clinical trials being conducted in their geographic area

• The Alzheimer’s Association’s Trial Match [https://www.alz.org/alzheimers-dementia/research_progress/clinical-trials/about-clinical-trials](https://www.alz.org/alzheimers-dementia/research_progress/clinical-trials/about-clinical-trials)
  – free, online resource that matches persons with dementia, caregivers, and healthy volunteers to clinical trials in their geographic area
Managing Sleep and Its Disorders: Beyond Sleep Hygiene

Descartes Li, MD
UCSF Professor of Psychiatry

We are such stuff
As dreams are made on, and our little life
Is rounded with a sleep

William Shakespeare, The Tempest
Outline

• Introduction
• Epidemiology
• Foundational concepts
• Diagnosis and assessment of sleep
• Treatment

Case Vignette

Jeff is a 54-year-old physician who reports that he awakens every morning at 4am no matter what time he goes to sleep. Extremely tired/sleepy mid-afternoon which makes it difficult to work productively.

What is the next best step in management?
Outline

- Introduction: Why do we sleep?
- Epidemiology
- Foundational concepts
- Diagnosis and assessment of sleep
- Treatment

Why do we sleep?

1. restoration
2. energy conservation,
3. processing and memory consolidation.
processing and memory consolidation

1. Even slugs need to sleep
2. If humans don’t sleep, learning is impaired


Outline

• Introduction
• Epidemiology: **Are we getting enough?**
• Foundational concepts
• Diagnosis and assessment of sleep
• Treatment
Sleep, those little slices of death — how I loathe them.
— Edgar Allan Poe

Industrialization and Hours of Sleep

• Society sleeps 1.5 hours less per hour per night compared to 100 years ago
  1942: average 7.9 hours per night
  2001: 6.7 hours per night

• The increase in work performance demanded by our 24 hour economy has effectively added a 13th month of work compared to the last century
“microsleeps”

Thirty-one percent (31%) of drivers will fall asleep while driving at least once in their lifetime.

→ 100,000 accidents a year happen because of tiredness.

Effect of technology on sleep

<table>
<thead>
<tr>
<th>52% believe they currently don't get enough sleep</th>
<th>22% say checking social media affects their ability to fall sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>15% struggle to avoid checking or sending late-night emails</td>
<td>18% admit just having their smartphone by their bed prevents them sleeping well</td>
</tr>
</tbody>
</table>

Blue Light blocking glasses
Doctors, after a 24 hour shift

- Experience a 1.5 to 2 SD deterioration in performance relative to baseline
- Make 300% more fatigue-related medical errors that lead to a patient’s death (5X as many serious diagnostic errors overall)
- Suffer 61% more needlestick and other sharp injuries
- Double their risk of an MVA
- Perform as if they have a BAC of 0.05 to 0.10%


Outline

- Introduction
- Epidemiology
- Foundational concepts
- Diagnosis and assessment of sleep
- Treatment
Opponent Process (or Two Process) Model of Sleep

- **Sleep Debt** and
- **Alerting Force** work at the same time
- **But they fluctuate independently**

At any given time, the sum is called **sleep propensity**

What is Sleep Debt?
(aka homeostatic drive or pressure)
What is the Alerting Force?
(aka Circadian rhythm)

Alerting Force

- cortisol
- adrenalin
- melatonin
- brain centers

TWO PROCESS MODEL OF SLEEP
Brain centers

Suprachiasmatic Nucleus (SCN)

Output Rhythms: Physiology Behavior

Light

Melatonin

Pituitary and Pineal Glands

Pituitary gland
Pons
Medulla oblongata
Spinal cord
Cerebellum

Pineal gland
Sleep tip:

Raise body temperature (early in the day)
Summary: Opponent Process Model of Sleep

- **Sleep Debt** and
- **Alerting Force** work at the same time
- **But they fluctuate independently**
Outline

• Introduction
• Epidemiology
• Foundational concepts
• **Diagnosis and assessment of sleep**
• Treatment

Test Question

62yo woman with sleep maintenance insomnia for the past six months. Self-prescribed trial of Unisom not helpful. What is the next best step in the management of this patient?

A. Assess for mood disorders and other comorbidities
B. Schedule for polysomnography
C. Require 2-week sleep diary
D. Give industry provided samples
E. Refer to a sleep medicine specialist
Test Question

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D. Give industry provided samples
E. Refer to a sleep medicine specialist

Evaluation of Insomnia or Hypersomnia

- Duration and natural history of symptoms
- Past and present medical & psychiatric history
- Medications & substances: prescription, non-prescription, “alternative” therapies
- Habits – alcohol, caffeine, nicotine
- Family history
- Lifestyle and stressors
- Rule out sleep apnea or periodic limb movements of sleep
### Four questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) How long does it usually take you to fall asleep?</td>
<td>Normal sleep latency is about 10 minutes; Be aware of patients with short latencies, such as 2 minutes</td>
</tr>
<tr>
<td>2) How many times a night do you wake up?</td>
<td>Ask this of the patient's sleep partner as well.</td>
</tr>
<tr>
<td>3) After each awakening, how long does it take to fall back asleep?</td>
<td>Combined with question #2 gives how much sleep is being lost</td>
</tr>
<tr>
<td>4) Do you feel refreshed upon awakening in the morning?</td>
<td>Most important question</td>
</tr>
</tbody>
</table>

*How much coffee do you drink?*

### Key Rule outs

- Obstructive sleep apnea
- Narcolepsy
- Restless leg syndrome
- Nocturnal myoclonus
- Caffeinism
Steve has difficulty initiating and maintaining sleep. He frequently naps, and drinks coffee or smokes cigarettes to maintain alertness during the day. His partner reports that he snores when he sleeps and often seems to stop breathing.

Obstructive Sleep Apnea Syndrome

- Witness apneas or snoring
- Excessive daytime sleepiness
- Morning headache and/or dry mouth
- Night sweats
- Morbid obesity
- Retrognathia
- Narrowed airway

Predisposing factors: middle-older age, male gender, obesity and use of CNS suppressants

Treatments: weight loss, avoidance of CNS depressants, continuous positive airway pressure (CPAP), dental devices, upper airway surgery and medications

Case

Jane was a good student throughout grade school and middle school. However, in high school, she was unable to stay awake during class, even when she had gotten plenty of sleep the night before.

Furthermore, if she were startled (for example, by a slamming locker door), she might collapse and be unable to move for a few minutes. In her freshman year she broke three pairs of glasses as a result of these bouts.

1. What are these bouts called?

Narcolepsy

- Narcolepsy pentad
  - Excessive daytime somnolence
  - Cataplexy
  - Hypnogogic hallucinations
  - Sleep paralysis
  - Disturbed nocturnal sleep
- Peak age of onset is adolescence
- Non-progressive and unrelenting course
- Associated with occupational and social impairments
- Associated with loss of hypocretin neurons
Case

Daphne is a 34-year-old woman with chief complaint of insomnia

- Frequent awakenings throughout the night. Although she aches and irritating discomfort in her legs during the evening
- Urgency to move her legs in order to alleviate discomfort. Moving her legs provides partial and temporary relief of the discomfort.
- Sensations are worse when she is at rest (i.e., lying or sitting down), and later in the day; they occur mainly during the evening and during the nighttime.
- When she takes a nap during the day, she is rarely bothered by these sensations.
Restless Legs Syndrome

- “Creepy”, “crawling” sensations in legs that are relieved by movement
- Generally idiopathic but can be secondary to uremia, iron deficiency anemia, and pregnancy
- Occurs both when awake and asleep
- Diagnosed with sleep study
- Often coexists with periodic limb movements in sleep (PLMS); the latter often lacks leg symptoms

periodic limb movements in sleep (PLMS)

- Previously known as Nocturnal Myoclonus
- Rhythmical extensions of the big toe and dorsiflexions of the ankle with occasional flexions of the knee and hip
- Lasts approximately 0.5-5.0 seconds
- Frequency of about one every 20-40 seconds
  - Clusters into episodes, each of which lasts several minutes or even hours
- Episodes are more numerous in the first half of the night
Treatment for Restless Legs Syndrome and Nocturnal Myoclonus

- Dopaminergic medications
- Benzodiazepines
- Opioids
- Anticonvulsants
- Others

Case Vignette

54-year-old physician reports that he awakens every morning at 4am no matter what time he goes to sleep. Extremely tired/sleepy mid-afternoon which makes it difficult to work productively. Drinks about five cups of coffee throughout the day to stay awake, but this seems to interfere with going to bed at a reasonable time.

How much caffeine is there in a cup of coffee?
What is the half-life of caffeine?
Caffeine

Can you drink coffee and then sleep?
Overuse can lead to restlessness, anxiety, cardiac arrhythmias, GI distress, irritability, etc

What about Non-caffeine stimulants?
Eg, modafanil (Provigil), methylphenidate

How much caffeine in the following products?

133mg
80mg
227mg
(per ounce, about 20)
How Much Caffeine?

(Starbucks Featured Dark Roast)

Vivarin
200mg/pill

Caffeine

- Dose ranges 200-500mg (OTC is 200 mg tabs)

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Caffeine content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starbucks Grande coffee (16 oz)</td>
<td>330mg</td>
</tr>
<tr>
<td>Panera coffee (16 oz)</td>
<td>189mg</td>
</tr>
<tr>
<td>McDonald's coffee (16 oz)</td>
<td>133mg</td>
</tr>
<tr>
<td>Red Bull (8 oz)</td>
<td>80mg (x2 for 16 oz)</td>
</tr>
<tr>
<td>Mountain Dew (16 oz)</td>
<td>72mg</td>
</tr>
<tr>
<td>Diet Coke (16 oz)</td>
<td>63mg</td>
</tr>
</tbody>
</table>
What is the half-life of caffeine?

Question: If you take 240mg of caffeine at 12noon, how much is still in your body at 10pm?

Half-life of caffeine = 3 to 7 hours (in healthy active individuals)

Answer: 60mg (which is the equivalent of 16oz of Diet Coke)

Assume ½ life = 5 hours

<table>
<thead>
<tr>
<th>Time</th>
<th>amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>12noon</td>
<td>240mg</td>
</tr>
<tr>
<td>5pm</td>
<td>120mg</td>
</tr>
<tr>
<td>10pm</td>
<td>60mg</td>
</tr>
</tbody>
</table>

What about another cup of coffee (133mg) at 3pm?

→ using formula above, that gives another 50mg at 10pm

Total = 60mg + 50mg = 110mg
Summary and Key Rule outs

• Obstructive sleep apnea
• Narcolepsy
• Restless leg syndrome
• Nocturnal myoclonus
• Caffeinism

Outline

• Introduction
• Epidemiology
• Foundational concepts
• Diagnosis and assessment of sleep
• Treatment
  – CBT-I
  – Pharmacotherapy
Test Question

62yo woman with sleep maintenance insomnia for the past six months. Self-prescribed trial of Unisom not helpful. No other medical or psychiatric morbidities. Which of the following is true*:

A. Moderate evidence for temazepam
B. Strong evidence for doxepin+suvorexant
C. Sufficient evidence for CBT-I as first line treatment
D. Moderate evidence that pharmacotherapy decisions should be independent of CBT-I

Nonpharmacologic Treatment Strategies: Sleep Hygiene

- Maintain regular bedtime and awakening time\(^1\)\(^-\)\(^3\)
- Exercise regularly, but not before bedtime\(^1\),\(^2\)
- Avoid naps\(^1\),\(^3\)
- Avoid caffeine intake after noon and alcohol and nicotine in the evening\(^1\),\(^2\)
- Make bedroom comfortable: dark, quiet, not too hot or too cold\(^1\),\(^2\)
- If hungry, have only a light snack before bedtime\(^2\)


Minimal evidence for sleep hygiene

“…the direct effects of individual recommendations on sleep remains largely untested in the general population.”


Sleep Hygiene is different from stimulus control and sleep restriction
Sleep Hygiene

If it worked, then the patient probably wouldn’t be coming to see you.

CBT-I for Bipolar Disorder: Treatment components

Case conceptualization: Night and Day
Stimulus control/sleep restriction*
Circadian/rhythm education
Pre-sleep ‘wind down’/ Roll bedtime forward by 20-30 mins per week
Brisk wakeup: overcoming sleep inertia
Unhelpful beliefs about sleep
Worry / rumination
Daytime focus
Strategies for different kinds of sleep disturbance
Attention to: Opportunity to sleep and Light/Dark

8 sessions, 90min each
Sleep Restriction Therapy

Rationale:
Aims to limit the person’s time in bed to the estimated average amount of nighttime sleep
- Goal 1: Maximize sleep efficiency
- Goal 2: Associate the bed with sleep
- Goal 3: Build homeostatic pressure to sleep

Stimulus Control Therapy

Rationale:
- Assumes there is a learned association between wakefulness and the bedroom
- To break this association the patient must not spend excessive time wide awake in the bedroom
**Stimulus Control Therapy**

- Go to bed only when sleepy
- Use the bed only for sleeping and sex – do not read, watch TV, or eat in bed
- If unable to sleep (in 20 mins), move to another room. Stay up until really sleepy. The goal is to associate the bed with falling asleep quickly
- Repeat tactic immediately above as often as necessary
- Awaken at the same time every morning regardless of total sleep time
- Do not nap


**Books on sleep**

![The Insomnia Answer](image)

*The Insomnia Answer*

Paul Gootsjer, Ph.D., and Arthur Spielman Ph.D.

![Why We Sleep](image)

*Why We Sleep*

Matthew Walker, PhD

NEW YORK TIMES BESTSELLER

UNLOCKING THE POWER OF SLEEP AND DREAMS

"Sleeping is the perfect combination of doing nothing and doing something. It’s not just black with nothing going on; it’s a state of alertness that enables us to give everything we need in life..." —Dr. Martin Monjan, Psychologist
What about sleep apps?

See also The Insomnia Answer, by P. Glovinsky and A. Spielman

<table>
<thead>
<tr>
<th>Program</th>
<th>Details</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restore</td>
<td>Offers computerized CBT-i as well as other cognitive-behavioral modules.</td>
<td>$125, one time</td>
</tr>
<tr>
<td>CBT for Insomnia</td>
<td>Old-school PDF and MP3 format. Allows users to contact a therapist in the premium version. Based on a proven approach, but not independently tested.</td>
<td>$50-$70, one time</td>
</tr>
<tr>
<td>CBT-I Coach</td>
<td>This app was designed to be used with a therapist, but a motivated patient can benefit from it solo. Created by the VA, but suitable for civilians.</td>
<td>Free</td>
</tr>
</tbody>
</table>

Outline

- Introduction
- Epidemiology
- Foundational concepts
- Diagnosis and assessment of sleep
- **Treatment**
  - CBT-I
  - Pharmacotherapy
Test Question

35yo man with sleep-onset (initial) insomnia. No h/o substance abuse, nor other psych d/o. Currently taking diphenhydramine, which is not helping. What next?

A. tiagabine
B. zolpidem
C. trazodone
D. melatonin
E. suvorexant

Test Question

35yo man with sleep-onset (initial) insomnia. No h/o substance abuse, nor other psych d/o. Currently taking diphenhydramine, which is not helping. What next?

A. tiagabine
B. **zolpidem**
C. trazodone
D. melatonin
E. suvorexant
Classes of hypnotics

Orexin receptor agonists: suvorexant (Belsomra)
Melatonin agonists: ramelteon (Rozerem)
BZD receptor agonist:
Eszopiclone (Lunesta)
Zolpidem (Ambien)
Zaleplon (Sonata)

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Anticonvulsants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heterocyclics</td>
<td>OTC Unisom</td>
</tr>
</tbody>
</table>
Test Question

Which of the following agents may be used for both sleep onset insomnia and sleep maintenance insomnia? (more than one may be correct)

A. eszopiclone
B. melatonin
C. ramelteon
D. Suvorexant
E. temazepam
F. trazodone
G. zolpidem
Table 4—Summary of clinical practice recommendations and GRADE components of decision-making

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
<th>Direction and Strength of Recommendation</th>
<th>Quality of Evidence</th>
<th>Benefits and Harms Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS receptor agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bz2A receptor agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>We suggest that clinicians use eszopiclone as a treatment for sleep onset and maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Very low</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>We suggest that clinicians use zolpidem as a treatment for sleep onset and maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Very low</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Meprobamate</td>
<td>We suggest that clinicians use meprobamate as a treatment for sleep onset and maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Very low</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Trifluperazine</td>
<td>We suggest that clinicians use trifluperazine as a treatment for sleep onset and maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Moderate</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Temazepam</td>
<td>We suggest that clinicians use temazepam as a treatment for sleep onset and maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Very low</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Melatonin agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramelteon</td>
<td>We suggest that clinicians use ramelteon as a treatment for sleep onset insomnia (versus no treatment) in adults.</td>
<td>WEAK Very low</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Heterocyclics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextrophan</td>
<td>We suggest that clinicians use dextrophan as a treatment for sleep maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Low</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>We suggest that clinicians not use trazodone as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Moderate</td>
<td>Harms outweigh benefits</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>We suggest that clinicians not use lamotrigine as a treatment for sleep onset insomnia (versus no treatment) in adults.</td>
<td>WEAK Very low</td>
<td>Benefits outweigh harms</td>
<td></td>
</tr>
<tr>
<td>Over-the-counter preparations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>We suggest that clinicians not use diphenhydramine as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Low</td>
<td>Benefits approx equal to harms</td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>We suggest that clinicians not use melatonin as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Very low</td>
<td>Benefits approx equal to harms</td>
<td></td>
</tr>
<tr>
<td>L-tryptophan</td>
<td>We suggest that clinicians not use L-tryptophan as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK High</td>
<td>Harms outweigh benefits</td>
<td></td>
</tr>
<tr>
<td>Valerian</td>
<td>We suggest that clinicians not use valerian as a treatment for sleep onset or sleep maintenance insomnia (versus no treatment) in adults.</td>
<td>WEAK Low</td>
<td>Benefits approx equal to harms</td>
<td></td>
</tr>
</tbody>
</table>

Case Vignette

54-year-old physician reports that he awakens every morning at 4am no matter what time he goes to sleep. Extremely tired/sleepy mid-afternoon which makes it difficult to work productively.

Doesn’t drink coffee

Has good sleep hygiene, even tried CBT-I

Has taken zolpidem and zaleplon with variable success

What medication could you try next?
Doxepin

- Best for early morning awakening or mid-insomnia
- Half life of 15 hours
- probably best to take only 3-4 nights per week


Doxepin: how to use

- Dissolve 10mg in 10cc syringe of water
- Take 2-3mg per night
- Complicating factors:
  - Long half-life (15 hours)
  - Tolerance
  - Decreased sleep debt
<table>
<thead>
<tr>
<th>Doxepin generic 10mg pills, #30</th>
<th>Silenor (doxepin) 3mg pills, #30</th>
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<td>$40</td>
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Outline

- Introduction
- Epidemiology
- Foundational concepts
- Diagnosis and assessment of sleep
- Treatment
  - CBT-I
  - Pharmacotherapy
Sleep is God, go worship

-Jim Butcher

Bonus material
Bonus: Light Therapy

Check out the Center for Environmental Therapeutics:  www.cet.org
Light boxes

Light therapy for MDD

- Daily exposure light box for 30 minutes ASAP after awakening, preferably between 7 and 8 am
  (Carex Day-Light Classic, emitting 4000-K white light rated at 10,000 lux at 35.56 cm from screen to cornea, with a UV filter)
- Patients used the light box at home and were given standardized verbal and written instructions.

A dramatic example of stimulus control:

Practice Makes Perfect

Harris J; Lack L; Kemp K; Wright H; Bootzin R. A randomized controlled trial of intensive sleep retraining (ISR): a brief conditioning treatment for chronic insomnia. SLEEP 2012;35(1):49-60.
50 sleep onset trials over a 25-h sleep deprivation period

- On day prior sleep restrict to 5 h (to increase homeostatic sleep drive)
- 9pm, subject arrives at sleep lab
- One treatment trial every 30min until 11pm the following night (50 trials)
- Each trial, pt allowed to fall asleep for 3min, then awoken and kept awake (reading or DVDs) until next trial
- Participants then had a recovery night’s sleep (maximum of 8 h).
Upcoming CME Courses

OCTOBER IN SAN FRANCISCO
Primary Care Medicine: Principles & Practice
Hotel Nikko, San Francisco
October 16 - 18, 2019

DECEMBER IN SAN FRANCISCO
Controversies in Women’s Health
Hotel Nikko, San Francisco
December 5 - 6, 2019

APRIL IN HAWAII
Primary Care Medicine: Update 2020
Wailea Marriott, Maui, Hawaii
April 5 - 10, 2020

JULY IN HAWAII
Essentials of Women’s Health: An Integrated Approach to Primary Care and Office Gynecology
July 5 - 10, 2020 (tentative)

AUGUST AT LAKE TAHOE
Essentials of Primary Care: A Core Curriculum for Adult Ambulatory Practice
Resort at Squaw Creek, North Lake Tahoe
August 2 - 7, 2020

All Courses Managed by:
UCSF Office of Continuing Medical Education
3333 California Street, Room 450, San Francisco, CA 94118
For attendee information call: 415-476-4251
For exhibitor information: 415-476-4253
Visit the web site at www.cme.ucsf.edu
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