Essential Evidence Milwaukee 2019
February 1, 2019

Learning Objectives

Discuss recent research important for family physicians and primary healthcare providers to update their diagnostic and treatment approaches to hypertension, depression, anxiety disorders, exercise and rehabilitation, genitourinary conditions, hyperlipidemia, acute respiratory infections, dementia and end of life care. Objectives for each presentation are listed at the beginning of each talk. The presentations are based on a literature review of recently published research studies and meta-analyses. Evidence sources include PubMed, InfoPoems and Cochrane systematic reviews. These updates are not intended to be comprehensive reviews but updates of the current knowledge base.

Faculty

Gary Ferenchick, MD, MS. is Professor of Medicine at Michigan State University College of Human Medicine, where he practices general internal medicine and is deeply involved in MSU-CHM major curriculum renovation. He earned his master's degree in human nutrition and medical degree from Michigan State University and completed his residency training in internal medicine at Michigan State University College of Human Medicine, where he has been a faculty member for over 25 year. Dr. Ferenchick is a Past-President of the Clerkship Directors in Internal Medicine. His research interest is the interface between medical education and information technology.

John Hickner, MD, MS. is Professor Emeritus at Michigan State University College of Human Medicine and recently retired from his post as Professor and Head of Family Medicine at the University of Illinois at Chicago. He is Editor-in-Chief of the *Journal of Family Practice*. After receiving his medical degree from Indiana University School of Medicine, Dr. Hickner completed his residency in family medicine at the Medical University of South Carolina and received a master's degree in Biostatistics and Research Design from the University of Michigan School of Public Health. He has been teaching evidence-based medicine to medical students, residents and practicing primary care physicians, nurse practitioners and physician assistants for over 20 years.

Speaker and Faculty Disclosures

John Hickner disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.
Gary Ferenchick disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.

Agenda for Essential Evidence Milwaukee

Friday, February 1, 2018

Information Mastery and Searching for Evidence: Key Points John Hickner, MD

Written by Mark Ebell, MD

Objectives

1. Learn the importance of patient-oriented evidence for interpreting medical studies
2. Learn an efficient way to search PubMed for clinically relevant information

Usefulness of medical information = (relevance x validity) / work

Relevance is a continuum:

Rat studies Surrogates Disease-specific All-cause mortality/QOL

Validity is a continuum:

Case study Case-control Cohort RCT Systematic review

Patient oriented evidence: anything that helps patients live a longer or better life.

Disease oriented evidence: everything else; surrogate or physiologic markers

POEM (Patient Oriented Evidence that Matters): a study that addresses a common or important condition, demonstrates improved patient oriented outcomes, and matters because it would change what we do.

Evidence-based sources to explore:

- Essential Evidence: www.essentialevidence.com
- Clinical Evidence: www.clinicalevidence.com
- Cochrane Library: www.cochrane.org
- DynaMed: www.dynamicmedical.com
- TRIP Database: www.tripdatabase.com
- Bandolier: www.medicine.ox.ac.uk/bandolier/
- National Guidelines Clearinghouse: www.guidelines.gov

Search hints

- Use Clinical Queries at the PubMed site
- Select “Narrow” filter
- Use quotes to narrow search to only those words appearing next to each other, i.e. “acute bronchitis” eliminates “acute exacerbation of chronic bronchitis”
- Combination of drug and disease is useful: “acute bronchitis” azithromycin; “infectious mononucleosis” corticosteroid; influenza osletamivir
- Optionally, “See all” and then add additional limits (English, abstract, human)
- Use “Not” terms to exclude groups of articles
- Then, select “Related articles” once you have a good hit.

HTN | 2019 Update Gary Ferenchick, MD

Learning objectives | Understand and apply:

1. The evolution of recommendations in BP management recommendations over the past 5 years
2. The results of the ACCORD BP, the HOPE – 3 and the SPRINT trial and their relevance for cardiovascular disease prevention.
3. AAFP and ACP guidelines on intensive BP treatment for those > 60
4. Review the 2017 AHA ACC guideline on HTN, and why the AAFP and ACP have chosen to not endorse it
5. The European Society of Cardiology 2018 hypertension guidelines

A lot has happened in the hypertension field since 2014, and honestly has become more confusing to patients and providers alike. If you feel like you have a good handle on the rapidly changing landscape of hypertension management you are doing extremely well.

The ACC/AHA guidelines were released in late 2017 have the potential to radically change how we approach HTN, however as you will see the AAFP and the ACP have chosen to not endorse these guidelines. Added to the mix is the late 2018 European Guidelines, which offer their own recommendations. Let's see if we can make sense of it all!

1: JNC 8

Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately. Patients want to be assured that blood pressure (BP) treatment will reduce their disease burden, while clinicians want guidance on hypertension management using the best scientific evidence. This report takes a rigorous, evidence-based approach to recommend treatment thresholds, goals, and medications in the management of hypertension in adults. Evidence was drawn from randomized controlled trials, which represent the gold standard for determining efficacy and effectiveness. Evidence quality and recommendations were graded based on their effect on important outcomes. There is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years. There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy. There is moderate evidence to support initial or add-on antihypertensive therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker in persons with CKD to improve kidney outcomes. Although this guideline provides evidence-based recommendations for the management of high BP and should meet the clinical needs of most patients, these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.

REFERENCE: *James PA et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8).* *JAMA. 2014 Feb 5;311 (5):507-20.*

2: The SPRINT Trial

BACKGROUND: The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.
METHODS: We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.
RESULTS: At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). Rates of serious adverse events

of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.
CONCLUSIONS: Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.
REFERENCE: *SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.*

3: The ACCORD BP Trial

BACKGROUND: There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants
with type 2 diabetes at high risk for cardiovascular events.
METHODS: A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.
RESULTS: After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P=0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001).
CONCLUSIONS: In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)
Reference*: ACCORD Study Group, Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1575-85. PMID: 20228401*

4: The Hope-3 Trial

BACKGROUND: Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.
METHODS: In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.
RESULTS: The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI,0.81 to 1.11; P=0.51). In one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had significantly lower rates of the first and second coprimary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P=0.02 and P=0.009, respectively, for trend in the two outcomes).
CONCLUSIONS: Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.).
REFERENCE: *Lonn EM, et al. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016 May 26;374(21):2009-20.*

Blood pressure recommendations in the post–SPRINT era

In January of 2017, the AAFP and the ACP jointly published a guideline based upon a systematic review of published randomized, controlled trials and observation studies (articles published through September of 2016 in Medline and January 2015 for other databases). There conclusions closely reflected the recommendations of the JNC 8. Importantly this means they has the results of the SPRINT Trial for this review.

5: AAFP/ACP: Practice guideline Intensive treatment for patients > 60

Description: The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) jointly developed this guideline to present the evidence and provide clinical recommendations based on the benefits and harms of higher versus lower blood pressure targets for the treatment of hypertension in adults aged 60 years or older.
Methods: This guideline is based on a systematic review of published randomized, controlled trials for primary outcomes and observational studies for harms only (identified through EMBASE, the Cochrane Database of Systematic Reviews, MEDLINE,and ClinicalTrials.gov), from database inception through January 2015. The MEDLINE search was updated through September2016. Evaluated outcomes included all-cause mortality, morbidity and mortality related to stroke, major cardiac events (fatal and nonfatal myocardial infarction and sudden cardiac death), and harms. This guideline grades the evidence and recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method.
Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes all adults aged 60 years or older with hypertension.
Recommendation 1: ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. (Grade: strong recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Recommendation 2: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Recommendation 3: ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (Grade: weak recommendation, low quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.
Reference: *Qaseen A et al. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017 Mar 21;166(6):430-437.*

It is now commonplace to recommend that lipid-lowering treatment be primarily based upon a patients' predicted cardiovascular disease risk rather than just the LDL cholesterol concentrations, thus essentially eliminating treatment thresholds that are based only on LDL cholesterol concentrations. This approach recognizes that the patients baseline risk "is a major determinant of the absolute benefits of statin treatment". This reflects a classic example of understanding how to apply baseline risk assessments in helping patients make treatment decisions.

As a theoretical example: if a given treatment reduces the risk of an event by 50%, an individual with a low baseline risk (e.g. 2%) has almost nothing to gain (this 50% decrease translates into a post treatment risk of 1% | NNT = 100). However, an individual with a moderate-high baseline risk (e.g. 20%) has more to gain (this 50% decrease translates into a post treatment risk of 10% | NNT = 10). Also, note that in each instance the relative risk reduction is the same.

Whether these levels of risk reduction are meaningful to the patient is where, of course, shared decision-making comes in.

In the new AHA/ACC guidelines, we are asked to use the 10-year cohort risk calculator much like we do for determining statin eligibility, to make therapeutic decisions for primary prevention in HTN. Abstract 6 support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.

6: Baseline predicted CV risk equations for DP lowering decisions

BACKGROUND: We aimed to investigate whether the benefits of blood pressure-lowering drugs are proportional to baseline cardiovascular risk, to establish whether absolute risk could be used to inform treatment decisions for blood pressure-lowering therapy, as is recommended for lipid-lowering therapy.

METHODS: This meta-analysis included individual participant data from trials that randomly assigned patients to either blood pressure-lowering drugs or placebo, or to more intensive or less intensive blood pressure-lowering regimens. The primary outcome was total major cardiovascular events, consisting of stroke, heart attack, heart failure, or cardiovascular death. Participants were separated into four categories of baseline 5-year major cardiovascular risk using a risk prediction equation developed from the placebo groups of the included trials (<11%, 11-15%, 15-21%, >21%).
FINDINGS: 11 trials and 26 randomised groups met the inclusion criteria, and included 67,475 individuals, of whom 51,917 had available data for the calculation of the risk equations. 4167 (8%) had a cardiovascular event during a median of 4·0 years (IQR 3·4-4·4) of follow-up. The mean estimated baseline levels of 5-year cardiovascular risk for each of the four risk groups were 6·0% (SD 2·0), 12·1% (1·5), 17·7% (1·7), and 26·8% (5·4). In each consecutive higher risk group, blood pressure-lowering treatment reduced the risk of cardiovascular events relatively by 18% (95% CI 7-27), 15% (4-25), 13% (2-22), and 15% (5-24), respectively (p=0·30 for trend). However, in absolute terms, treating 1000 patients in each group with blood pressure-lowering treatment for 5 years would prevent 14 (95% CI 8-21), 20 (8-31), 24 (8-40), and 38 (16-61) cardiovascular events, respectively (p=0·04 for trend).
INTERPRETATION: Lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions as baseline risk increases. These results support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.
REFERENCE: *Blood Pressure Lowering Treatment Trialists' Collaboration, Sundström J, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014 Aug 16;384(9943):591-8.*

ACC AHA Guidelines My Quick Review

The following is a quick review of the ACC AHA Class of Recommendation (COR) and Level of evidence (LOE) that is now used for all ACC/AHA Guidelines. They are meant of assist us and our patients in decision-making. Note the primary differences from the previous paradigm is separating Level B and Level C evidence based upon the quality of the underlying data.

Class (Strength) of Recommendation (COR) Table

- **Class I (Benefit >>> Risk):** **Should be done | *Is* useful | (Strong)**
- Class IIa (Benefit >> Risk): Reasonable to do | *Can* be useful | (Moderate)
- Class IIb (Benefit ≥ Risk): May be considered | *Unknown* usefulness (Weak)
- Class III (No benefit or harm): Not helpful or harmful

Level (Quality) of Evidence (LOE)

- Level A:
  - High quality evidence from ≥ 1 RCT
  - Meta-analysis of high-quality RCTs
  - ≥ 1 RCT corroborated by high-quality registry studies
- Level B-R (Randomized):
  - Moderate quality evidence from ≥ 1 RCT
  - Meta-analyses of moderate quality RCTs
- Level B-NR (Non-randomized):
  - Moderate quality evidence from ≥ 1 high-quality nonrandomized/observational or registry studies
  - Meta-analyses of such studies
- Level C-LD
  - Randomized or nonrandomized/observational or registry studies with limitations of design or execution
  - Meta-analyses of such studies
  - Physiological or mechanistic studies in humans
- Level C-EO
  - Consensus opinion based upon clinical experience

The COR and LOE are determined independent of each other. Any COR can be paired with any LOE (notably LOE C does not imply the COR is weak)

2107 ACC AHA Guidelines on HTN

In November of 2017, the American College of Cardiology/American Heart Association published a new guideline on the prevention, detection, evaluation, and management of high blood pressure in adults. The article was published online and is 41 pages, 106 recommendations and 23 tables; however, the "meat" of the guideline was covered in only ~ 89 pages. Also the COI declarations covered 22 pages (on a quick review however, most authors had no COI with industry). Articles published through August of 2015 were included. This guideline was heavily influenced by results of the SPRINT study.

Broad sections included the following:

- BP and CVD risk
- Classification of the BP
- Measurement of BP
- Causes of HTN
- Patient Evaluation
- Treatment of High BP
- Hypertension in patients with comorbidities
- Special patient groups
- Other considerations (e.g. resistant HTN, hypertensive crises etc)

I'm including my determination of the items that are most relevant for primary care providers. *My Summary* of key aspects of the New BP guidelines are below the numbering and emphases are mine

The New Normal

1. BP should be categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP (Table 6) (COR I | LOE B-NR)

The new normal is < 120 / < 80. In addition, a new category of "Elevated Blood Pressure" is included (i.e. 120 – 129 / < 80; and if present, non-pharmacological therapy is recommended).

Hypertension is defined now as > 130 / > 80. Also returned from previous guidelines are stages of hypertension (Stage 1 and Stage 2). Note the checklist for accurate BP measurement from this guideline is in the appendix

BP Category	SBP		DBP
Normal	< 120	and	< 80
Elevated	120-129	and	< 80
Hypertension			
• Stage 1	130-139	or	80 - 89

• Stage 2	> 140	or	> 90

Out-of-office BP measurements recommended

2. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions. (COR I | LOE A)

Take at least two readings 1 min apart in morning before taking medications and in evening before supper. Optimally, measure and record BP daily. Ideally, obtain weekly BP readings beginning 2 weeks after a change in the treatment regimen and during the week before a clinic visit. BP should be based on an average of readings on ≥2 occasions for clinical decision-making.

Also note that the UPSTF "recommends obtaining measurements outside of the clinical setting for diagnostic confirmation before starting treatment".

- "The USPSTF found convincing evidence that ABPM is the best method (i.e. reference standard) for diagnosing hypertension."
- "Good-quality evidence suggests that confirmation of hypertension with HBPM (with appropriate protocols) may be acceptable."
    - However the evidence is not as substantial as it is for ABPM

The information above may be reinforced with videos available online: Monitoring Your Blood Pressure at Home.

Treatment recommendations are a bit more nuanced

3. Use of BP-lowering medications is recommended for **secondary prevention** of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for **primary prevention** in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher. (COR I | LOE A for SBP)
4. Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk <10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher. (COR I | LOE C-LD)

Use the ACC/AHA Pooled Cohort Equation to estimate 10-year risk of atherosclerotic CVD. However – with one exception (as noted in the blue cell below) treatment should be initiated with a confirmed BP of ≥ 130 / ≥ 80. You will note that for most patients we are asked to calculated the 10-year ASCVD risk (much like we are asked to do for determining candidacy for statin therapy) to determine if the patients 10-year risk is > or < 10%

Summary of BP Thresholds and Goals for Pharmacologic Treatment		
Clinical Condition(s)	**BP Threshold, mm**	**Hg BP Goal, mm Hg**

General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized,	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
Chronic kidney disease	≥130/80	<130/80
Chronic kidney disease after renal transplantation	≥130/80	<130/80
Heart failure	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥130/80	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

5. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. (COR I | LOE A)
6. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. (COR I | LOE C-EO)

Special Circumstances

Stable ischemic Heart Dz (SIHD)

7. Adults with SIHD and hypertension (BP ≥130/80 mm Hg) should be treated with medications (e.g., **GDMT beta blockers**, ACE inhibitors, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or **mineralocorticoid receptor antagonists**) as needed to further control hypertension

Heart Failure with Preserved Ejection Fraction

8. Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and **beta blockers** titrated to attain SBP of less than 130 mm Hg. (COR I | C-LD)

Note that GDMT beta-blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta-blockers with intrinsic sympathomimetic activity (e.g. pindolol, acebutolol). The beta-blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.

Diabetes

9. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective (COR I | LOE A)
10. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria (COR IIb | LOE B-NR)

African-Americans

11. In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (COR I | B-R)
12. Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension. (COR I | C-LD)

Elderly (> 65)

13. Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher (COR I | LOE A)
14. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. (COR IIa | LOE C-EO)

According to data from NHANEs published in the guideline, the prevalence of HTN will triple for men and double for women under the age of 45 (a group of patients not well represented in trials of aggressive BP lowering). (Ann Intern Med 2017); Recall that the average of the participants in the SPRINT trial was 50.

7: 13.7% *more* people in the US are now classified as having HTN

BACKGROUND: The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults provides recommendations for the definition of hypertension, systolic and diastolic blood pressure (BP) thresholds for initiation of antihypertensive medication and BP target goals.
OBJECTIVE: Determine the prevalence of hypertension, implications of recommendations for antihypertensive medication and prevalence of BP above the treatment goal among US adults using criteria from the 2017 ACC/AHA and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines.
METHODS: We analyzed data from the 2011-2014 National Health and Nutrition Examination Survey (N=9,623). **NHANES** participants completed study interviews and an examination. For each participant, blood pressure was measured three times following a standardized protocol and averaged. Results were weighted to produce
US population estimates.
RESULTS: According to the 2017 ACC/AHA and JNC7 guidelines, the overall crude prevalence of hypertension among US adults was 45.6% (95% confidence interval [CI] 43.6%,47.6%) and 31.9% (95%CI 30.1%, 33.7%), respectively, and antihypertensive medication was recommended for 36.2% (95%CI 34.2%, 38.2%) and 34.3% (32.5%, 36.2%) of US adults, respectively. Compared to US adults recommended antihypertensive medication by JNC7, those recommended treatment by the 2017 ACC/AHA guideline but not JNC7 had higher CVD risk. Non-pharmacological intervention is advised for the 9.4% of US adults with hypertension according to the 2017 ACC/AHA guideline who are not recommended antihypertensive medication. Among US adults taking antihypertensive medication,

53.4% (95%CI 49.9%, 56.8%) and 39.0% (95%CI 36.4%, 41.6%) had BP above the treatment goal according to the 2017 ACC/AHA and JNC7 guidelines, respectively. Overall, 103.3 (95%CI 92.7,114.0) million US adults had hypertension according to the 2017 ACC/AHA guideline of whom 81.9 (95%CI 73.8, 90.1) million were recommended antihypertensive medication.
CONCLUSION: Compared with the JNC 7 guideline, the 2017 ACC/AHA guideline results in a substantial increase in the prevalence of hypertension but a small increase in the percentage of U.S. adults recommended antihypertensive medication. A substantial proportion of US adults taking antihypertensive medication is recommended more intensive BP lowering under the 2017 ACC/AHA guideline.
***REFERENCE**: Muntner P et al. Potential U.S. Population Impact of the 2017 American College of Cardiology/American Heart Association High Blood Pressure Guideline.J Am Coll Cardiol. 2017 Nov 6.(PMID: 29146532)*

Cochrane Reviews

The following abstracts were published in the Cochrane reviews in 2017 and 2018, for brevity purposes I included only the conclusions, which were a combination of the authors, published conclusions with my additions from the results section.

8: In healthy adults a small net benefit of treating BP > 140 / > 90

CONCLUSIONS: In 7 studies (17,327 patients, mean age of 50 and mean BP of 160/98, 5 years of follow up) antihypertensive drugs (compared to placebo or no therapy) used to treat predominantly healthy adults aged 18 to 59 years with mild to moderate primary hypertension (SBP > 140 OR DBP >90) have a small absolute effect to reduce cardiovascular mortality and morbidity primarily due to reduction in cerebrovascular mortality and morbidity (0.6% vs 1.3%). All-cause mortality (2.3 vs 2.4%) and coronary heart disease were not reduced. There is lack of good evidence on withdrawal due to adverse events. Future trials in this age group should be at least 10 years in duration and should compare different first-line drug classes and strategies.
***REERENCE:** Musini VM et al. Pharmacotherapy for hypertension in adults aged 18 to 59 years. Cochrane Database Syst Rev. 2017 Aug 16;8:CD008276.*

9: In adults with CV Dz, no benefit in lower (<135/<85) vs higher BP targets

CONCLUSIONS: We found no evidence of a difference in total mortality, serious adverse events, or total cardiovascular events between people with hypertension and cardiovascular disease treated to a lower or to a standard blood pressure target. This suggests that no net health benefit is derived from a lower systolic blood pressure target. We found very limited evidence on adverse events, which led to high uncertainty. At present, evidence is insufficient to justify lower blood pressure targets (≤ 135/85 mmHg) in people with hypertension and established cardiovascular disease. More trials are needed to examine this topic.
***REFERENCE:** Saiz LC, et al. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database Syst Rev. 2018 Jul 20;7:CD010315*

10: In older adults, BP target of < 140/ <90 of uncertain benefit

CONCLUSIONS: In 3 unblinded randomized trials of 8221 hypertensive adults mean ag 74.8, higher BP targets 150-160/90 compared to lower targets of 140/90 followed for 2 - 4 years demonstrated a no significant difference in all-cause mortality (RR 1,24) stroke (RR 1.25) total CV serious events (RR 1.19). However, the 95% confidence intervals of these outcomes suggest the lower BP target is probably not worse and might offer a clinically important benefit. At the present time there is insufficient evidence to know whether a higher BP target (range 150 to 160 / 95 to 105 mmHg) or a lower BP target (less than 140/90 mmHg) is better for older adults with high BP. Data on adverse effects were not available from all trials and not different, including total serious adverse events, total minor adverse events, and withdrawals due to adverse effects. Additional good-quality trials assessing BP targets in this population are needed.
REFERENCE: Garrison SR et al. Blood pressure targets for hypertension in older adults. Cochrane Database Syst Rev. 2017 Aug 8;8:CD011575.

11: In patients with stroke or TIA use of ACE or diuretic supported, uncertain optimal SBP

Conclusions: Our results support the use of BPLDs in people with stroke or TIA for reducing the risk of recurrent stroke. Current evidence is primarily derived from trials studying an ACE inhibitor or a diuretic. No definite conclusions can be drawn from current evidence regarding an optimal systolic blood pressure target after stroke or TIA.
***REFERENCE:** Zonneveld TP et al. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. Cochrane Database Syst Rev. 2018 Jul 19;7:CD007858.*

12: First line drugs for HTN

AUTHORS' CONCLUSIONS: First-line low-dose thiazides reduced all morbidity and mortality outcomes in adult patients with moderate to severe primary hypertension. First-line ACE inhibitors and calcium channel blockers may be similarly effective, but the evidence was of lower quality. First-line high-dose thiazides and first-line beta-blockers were inferior to first-line low-dose thiazides.
REFERENCE: *Wright JM et al. First-line drugs for hypertension. Cochrane Database Syst Rev. 2018 Apr 18;4:CD001841.*

AAFP does not endorse the new AHA/ACC HTN guidelines …..

In Mid-December 2017, the AAFP decided to not endorse the AHA/ACC HTN guidelines, but to continue to endorse the 2014 JNC8 guideline. The AAFP was not involved in the development of the guidelines. The chair of the AAFP's Commission on Health of the Public and Science (CHPS), David O'Gurek, M.D. stated that the AAFP used the same process to review both the JNC 8 and the AHA/ACC Guidelines, and concluded that the 2017 guidelines "didn't meet the Academy's criteria for endorsement or affirmation of value," and that "JNC8 upheld the scientific rigor that provided strong recommendations to family physicians and patients on appropriate treatment of hypertension."
Reasons for non-endorsement included the contention that:

- The bulk of the guideline was not based on a systematic evidence review
    - A systematic review was performed for 4 key questions, although the guideline provided over 100 recommendations
    - Assessments of the quality of individual studies or systematic reviews weren't provided
    - Specifically "…the guideline offered a strong recommendation (COR: I) for using the unvalidated atherosclerotic cardiovascular disease risk assessment tool previously developed by AHA and ACC to determine whether medications should be initiated for BP control. However, this recommendation wasn't based on evidence that using the tool in this way improves outcomes."
- Substantial weight was given to the SPRINT trial, while other trials were minimized
    - The AAFP "… commission said conflict of interest is a major concern in judging the trustworthiness of guidelines and plays a key role in the AAFP's assessment of guidelines. In the case of the AHA/ACC guideline, the guideline panel commissioned the chair of the SPRINT trial steering committee to chair its work, when, notably, the SPRINT trial served as the foundation for the guideline panel's recommendations to change BP treatment targets."
- Additionally "… several other AHA/ACC guideline panel members had intellectual conflicts of interest, which were not considered in the guideline's preparation."
    - "The AAFP chose not to participate in this guideline development given significant concerns about the guideline methodology, including the management of intellectual conflicts of interest of guideline participants"
- The harms of treating patients to a lower BP were not assessed in the systematic review.

"With competing guidelines and recommendations, family physicians, as bold champions of science, have an opportunity to be a guiding light in the darkness of confusion to deliver quality care that's grounded in science and is patient-centered," O'Gurek concluded.
AAFP News Accessed Online December 26th 2017
https://www.aafp.org/news/health-of-the-public/20171212notendorseaha-accgdlne.html

…… Neither does the ACP

Wilt T et al, for the Clinical Guidelines Committee of the American College of Physicians. Hypertension Limbo: Balancing Benefits, Harms, and Patient Preferences Before We Lower the Bar on Blood Pressure. Annals of Internal Medicine 2018;168:

Timothy Wilt for the Clinical Guidelines Committee of the American College of Physicians "... the (ACC/AHA) guideline falls short in weighing the potential benefits against potential harms, costs, and anticipated variation in individual patient preferences."

"Are the harms, costs, and complexity of care associated with this new target justified by the presumed benefits of labeling nearly half the U.S. population as unwell and subjecting them to treatment? We think not and believe that many primary care providers and patients would agree. The ACC/AHA based the new definition primarily on selected observational studies showing an association between a BP above 130/80 mm Hg and elevated cardiovascular risk, but few empirical data show that treating to this target in the general population will improve outcomes."

"It is important to consider the ramifications of labeling asymptomatic persons as unwell before expanding a disease definition"

"We believe that initiation of pharmacologic therapy at or above a BP of 130/80 mm Hg and treatment to targets less than 130/80 mm Hg in a broad population of older adults are not supported by evidence and may result in low-value care for several reasons."

"SPRINT provides the footing for an intensive treatment target in higher-risk populations, but the lack of consistent benefit across trials underscores the uncertainty about the actual benefit of aggressive control and highlights the need for targeted application of the SPRINT findings"

"In addition, the assumption that data from trials in patients with established hypertension applies to newly diagnosed patients is flawed"

"Third, there is no evidence from randomized controlled trials to support a DBP target less than 80 mm Hg."

"Clinical policy focused on lower SBP targets should permit a choice based on a patient's risk profile, susceptibility to harms, and treatment preferences."

European Guidelines 2018

In late 2018, the European Guidelines were published (ESC/ESH Guidelines for the management of arterial hypertension). This was a very large document and without going into all of the details, I just want to show how these guidelines “stack up” against the others discussed in this chapter. Primarily their definition of hypertension is consistent with the JNC VIII and not the ACC. However, they do endorse the idea of staging of BP (a concept not mentioned in the JNC VIII guideline)

REFERENCE: Williams B, Mancia et al for the ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-3104.

REFERENCE: Whelton PK(1)(2), Williams B(3)(4). The 2018 European Society of Cardiology/European Society of Hypertension and 2017 American College of Cardiology/American Heart Association Blood Pressure Guidelines: More Similar Than Different. JAMA. 2018 Nov 6;320(17):1749-1750.

JNC VIII	ACC/AHA	ACP/AAFP	European Society of Cardiology/ HTN

BP Category				
Optimal				< 120 / <80
Normal		> 140 / > 90	> 140 / > 90	120 -129 / 80 - 84
Elevated***		> 140 / > 90		130-139 / 85 - 89**
Hypertension	> 140 / > 90		> 140 / > 90	
Stage 1		> 140 / > 90		140 -159 / 90 – 99
Stage 2		> 140 / > 90		160 - 179 / 100 - 109
Stage 3				≥ 180 / ≥ 110

*** > 150 / > 90 for those > 60**

**** Consider drug treatment if CV risk is very high (i.e. CVD – including asymptomatic disease on imaging, DM, Grade 3 HTN, CKD)**

***** Called High Normal in ECS Guideline**

The following two observational studies essentially come to opposite conclusions. Abstract 13 demonstrated no association between treating and not treating a blood pressure of 140-159/90-99 (Stage 2 HTN according to the ACC/AHA guidelines) in low risk individuals aged 18 – 74 and rates of mortality or cardiovascular disease after 5.8 years, but treatment was associated with higher risks of syncope, electrolyte abnormalities and acute kidney injury. Abstract 14 did demonstrate an association between elevated blood pressure (> 120/ >80) and subsequent adverse cardiovascular outcomes in young adults (mean age 35).

13: Treating patient with low risk mild HTN (untreated SBP 140 – 159 / 90 – 99) of uncertain benefit after a 6 year follow up

Importance: Evidence to support initiation of pharmacologic treatment in low-risk patients with mild hypertension is inconclusive, with previous trials underpowered to demonstrate benefit. Clinical guidelines across the world are contradictory.
Objective: To examine whether antihypertensive treatment is associated with a low risk of mortality and cardiovascular disease (CVD) in low-risk patients with mild hypertension.
Design, Setting, and Participants: In this longitudinal cohort study, data were extracted from the Clinical Practice Research Datalink, from January 1, 1998, through September 30, 2015, for patients aged 18 to 74 years who had mild hypertension (untreated blood pressure of 140/90-159/99 mm Hg) and no previous treatment. Anyone with a history of CVD or CVD risk factors was excluded. Patients exited the cohort if follow-up records became unavailable or they experienced an outcome of interest.
Exposures: Prescription of antihypertensive medication. Propensity scores for likelihood of treatment were constructed using a logistic regression model. Individuals treated within 12 months of diagnosis were matched to untreated patients by propensity score using the nearest-neighbor method.
Main Outcomes and Measures: The rates of mortality, CVD, and adverse events among patients prescribed antihypertensive treatment at baseline, compared with those who were not prescribed such treatment, using Cox proportional hazards regression.
Results: A total of 19 143 treated patients (mean [SD] age, 54.7 [11.8] years; 10 705 [55.9%] women; 10 629 [55.5%] white) were matched to 19 143 similar untreated patients (mean [SD] age, 54.9 [12.2] years; 10 631 [55.5%] female; 10 654 [55.7%] white). During a median follow-up period of 5.8 years (interquartile range, 2.6-9.0 years), no evidence of an association was found between antihypertensive treatment and mortality (hazard ratio [HR], 1.02; 95% CI, 0.88-1.17) or between antihypertensive treatment and CVD (HR, 1.09; 95% CI, 0.95-1.25). Treatment was associated with an increased risk of adverse events, including hypotension (HR, 1.69; 95% CI, 1.30-2.20; number needed to harm at 10 years [NNH10], 41), syncope (HR, 1.28; 95% CI, 1.10-1.50; NNH10, 35), electrolyte abnormalities (HR, 1.72; 95% CI, 1.12-2.65; NNH10, 111), and acute kidney injury (HR, 1.37; 95% CI, 1.00-1.88; NNH10, 91).

Conclusions and Relevance: This prespecified analysis found no evidence to support guideline recommendations that encourage initiation of treatment in patients with low-risk mild hypertension. There was evidence of an increased risk of adverse events, which suggests that physicians should exercise caution when following guidelines that generalize findings from trials conducted in high-risk individuals to those at lower risk.
REFERENCE: *Sheppard JP et al. Benefits and Harms of Antihypertensive Treatment in Low-Risk Patients With Mild Hypertension. JAMA Intern Med. 2018 Oct 29. doi: 10.1001/jamainternmed.2018.4684.*

14: HTN (ACC criteria) in those < 40 associated with worse event rates on 18 years of follow up

Importance: Little is known regarding the association between level of blood pressure (BP) in young adulthood and cardiovascular disease (CVD) events by middle age.
Objective: To assess whether young adults who developed hypertension, defined by the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) BP guideline, before age 40 years have higher risk for CVD events compared with those who maintained normal BP.
Design, Setting, and Participants: Analyses were conducted in the prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) study, started in March 1985. CARDIA enrolled 5115 African American and white participants aged 18 to 30 years from 4 US field centers (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). Outcomes were available through August 2015.
Exposures: Using the highest BP measured from the first examination to the examination closest to, but not after, age 40 years, each participant was categorized as having normal BP (untreated systolic BP [SBP] <120 mm Hg and diastolic BP [DBP] <80 mm Hg; n = 2574); elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg; n = 445); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg; n = 1194); or stage 2 hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg, or taking antihypertensive medication; n = 638).
Main Outcomes and Measures: CVD events: fatal and nonfatal coronary heart disease (CHD), heart failure, stroke, transient ischemic attack, or intervention for peripheral artery disease (PAD).
Results: The final cohort included 4851 adults (mean age when follow-up for outcomes began, 35.7 years [SD, 3.6]; 2657 women [55%]; 2441 African American [50%]; 206 taking antihypertensive medication [4%]). Over a median follow-up of 18.8 years, 228 incident CVD events occurred (CHD, 109; stroke, 63; heart failure, 48; PAD, 8). CVD incidence rates for normal BP, elevated BP, stage 1 hypertension, and stage 2 hypertension were 1.37 (95% CI, 1.07-1.75), 2.74 (95% CI, 1.78-4.20), 3.15 (95% CI, 2.47-4.02), and 8.04 (95% CI, 6.45-10.03) per 1000 person-years, respectively. After multivariable adjustment, hazard ratios for CVD events for elevated BP, stage 1 hypertension, and stage 2 hypertension vs normal BP were 1.67 (95% CI, 1.01-2.77), 1.75 (95% CI, 1.22-2.53), and 3.49 (95% CI, 2.42-5.05), respectively.
Conclusions and Relevance: Among young adults, those with elevated blood pressure, stage 1 hypertension, and stage 2 hypertension before age 40 years, as defined by the blood pressure classification in the 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, had significantly higher risk for subsequent cardiovascular disease events compared with those with normal blood pressure before age 40 years. The ACC/AHA blood pressure classification system may help identify young adults at higher risk for cardiovascular disease events.
Reference: *Yano Y et al. Association of Blood Pressure Classification in Young Adults Using the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline With Cardiovascular Events Later in Life. JAMA. 2018 Nov 6;320(17):1774-1782.*
Comment in. JAMA. 2018 Nov 6;320(17):1760-1763. /NEJMe1802369

Bottom Lines

1. The JNC 8 (published in 2014) recommends treatment for BP when it is > 140/>90 in patients < 60 and>150/>90 in patients over 60.
2. The SPRNT trial demonstrated that in a select group of high-risk hypertensive patients, treating to a BP target of ~ 120/80 is associated with fewer adverse CV event and mortality (NNT ~ 90) but more harm (NNH -=45) and higher medication burden, but did not include diabetics or patients with cerebrovascular disease
3. The AAFP and ACP jointly published a guideline in 2017 essentially endorsing the JNC 8 recommendations of treating a blood pressure of >150/>90 for those over the age of 60
4. The AHA ACC guideline published in late 2017 recommended treatment at a threshold of 130/80 for almost all adult patients (the exception is a treatment threshold of 140/90for lower risk patients
5. The AAFP and the ACP have not endorsed the AHA ACC guideline
6. Neither has the201 European Guidelines
7. Treating low risk patients with blood pressures of 140-159/90-99 is of uncertain benefit

Depression and Anxiety — John Hickner, MD

Objectives

1. Review recent studies on prevention and treatment of depression
2. Review recent studies on the treatment of anxiety disorders
3. Review evidence of effectiveness for mindfulness-based therapy and internet-based therapy for mental health disorders

Depression

1. Effect of physical activity on risk for depression

Clinical question: Is physical activity at baseline associated with a reduced risk of subsequent incident depression?
Study design: Meta-analysis (other)
Funding source: Unknown/not stated
Setting: Various (meta-analysis)
Synopsis: For this meta-analysis of prospective cohort studies the authors included 49 studies without overlapping populations. The studies included a total of 266,939 individuals who were followed up for more than 1.8 million person-years. Men and women were nearly equally represented (47% and 53%, respectively). Studies were included if: the participants were free of depression or threshold depressive symptoms as measured by any of several tools; physical activity was measured (generally with a self-report questionnaire); the study was a prospective cohort design with at least one year of follow-up (average 7.4 years); and the study evaluated incident depression as an outcome (various methods). Higher physical activity was considered to be more than 150 minutes per week of at least moderate-intensity activity, such as brisk walking. People with higher levels of physical activity were less likely to have incident depression (adjusted odds ratio 0.83; 95% CI 0.79 - 0.88; P < .001). Several potential confounders (including age, sex, body mass index, smoking, and baseline [subthreshold] depressive symptoms) were considered and did not significantly change the results. Subgroup analyses by age group (< 18 years, 18 – 65 years, > 65 years) showed no significant differences from the baseline analysis.
Bottom line: This was a large meta-analysis of prospective cohort studies of individuals of all ages without depression at baseline. All of the studies included at least one year of follow-up. People with high physical activity (> 150 minutes per week of at least moderate-intensity activity) were less likely to have subsequent incident depression than those who had low levels of physical activity. Given the large size of the population, the prospective nature of the studies, and the consistency across age groups, the suggestion that exercise is a preventive factor for new onset depression is relatively strong. This is further evidence that exercise is medicine. (LOE = 2a)
Schuch FB, Vancampfort D, Firth J, et al. Physical activity and incident depression: a meta-analysis of prospective cohort studies. Am J Psychiatry 2018;175(7):631-648.

2. HRT to prevent depression in peri- and early menopause

Clinical question: Is hormone replacement therapy with estrogen and progesterone effective for preventing symptoms of depression in perimenopausal and early postmenopausal women?
Study design: Randomized controlled trial (double-blinded)
Funding source: Foundation
Allocation: Uncertain
Setting: Outpatient (specialty)
Synopsis: These investigators identified women (N = 172), aged 45 to 60 years, who were medically healthy and euthymic at study enrollment according to standard diagnostic criteria. Eligible women randomly received (uncertain allocation concealment) 0.1 mg transdermal estradiol daily for 12 months and 200 mg oral micronized progesterone daily for 12 days every 2 to 3 months or matched placebo. Depressive symptoms were assessed using a validated diagnostic tool at months 1, 2, 4, 6, 8, 10, and 12. Individuals who assessed outcomes remained masked to treatment group assignment. Complete follow-up occurred for 76% of participants at 12 months, with 85% follow-up for at least 4 visits. Using intention-to-treat analysis, clinically significant depressive symptoms developed in fewer women assigned to active treatment than to the control group (17.3% vs 32.3%; number needed to treat = 6.6; 95% CI 3.6 - 46.5). In secondary analysis, mood benefits were most evident among women in the early perimenopause transition and among those with an increased number of stressful life events in the 6 months preceding study enrollment. Baseline estrogen levels, vasomotor symptom severity, history of depression, and history of abuse did not affect treatment effects. Adverse effects due to vaginal bleeding occurred significantly more often in the treatment group, but drop-out rates were similar between the 2 groups.
Bottom line: Hormone replacement therapy with transdermal estrogen and episodic oral progesterone for 12 months significantly reduced clinically relevant depressive symptoms in initially euthymic perimenopausal and early postmenopausal women. The benefit was most pronounced in women in the early perimenopausal transition and in women who reported an increased number of stressful life events prior to treatment. Neither severity of vasomotor symptoms nor a history of depression affected the likelihood of a treatment benefit. (LOE = 1b)
Gordon JL, Rubinow DR, Eisenlohr-Moul TA, Xia K, Schmidt PJ, Girdler SS. Efficacy of transdermal estradiol and micronized progesterone in the prevention of depressive symptoms in the menopause transition. A randomized clinical trial. JAMA Psychiatry 2018;75(2):149-157.

3. Comparing CBT & light therapy for seasonal affective disorder (SAD)

Clinical question: How does cognitive-behavioral therapy compare to light therapy for treatment of seasonal affective disorder?
Study design: Randomized controlled trial (non-blinded)
Allocation: Concealed
Funding source: Government
Setting: Outpatient (any)
Synopsis: In this randomized controlled trial 177 patients with current diagnosis of seasonal affective disorder (SAD) were randomized to either CBT-SAD or light therapy. Participants were adult community volunteers recruited in fall and winter months through local media in Vermont (44.5 degrees north) and referrals from health clinics. Inclusion criteria were diagnosis of depression based on DSM-IV-TR criteria, a current SAD episode, and either no use or stable use of antidepressant medications. Participants were excluded if they were in current psychotherapy or light therapy, had prior light therapy or CBT for SAD, had serious mental illness requiring acute treatment (e.g. psychosis, suicidality) or hypothyroidism, or had plans to leave the area for more than one week through March. Allocation was concealed and outcome assessment was blinded. The 6-week treatment period had to commence by the first week of February. Light therapy was with a source providing 10,000 lux of cool fluorescent light through an ultraviolet filter, started at 30 minutes daily in the morning and adjusted according to a protocol if needed. CBT was specifically tailored to SAD and provided in groups of 4-8 participants by one of three therapists in 2 90-minute sessions weekly for 6 weeks. Drop-outs were higher in the CPT group (13/88) vs the light group (1/89). Remission as assessed using two different tools, SIGH-SAD and BDI-II, did not differ between groups at the end of the study period. About half of participants in each group achieved remission. The proportion in remission difference between light therapy and CBT-SAD was small, but clinically insignificant (0.004 for SIGH-SAD, and 0.076 for BDI-II).
Bottom line: Cognitive-behavioral therapy for seasonal affective disorder (CBT-SAD) provided to small groups of patients for 18 hours over 6 weeks is as effective as daily light therapy for the treatment of seasonal affective disorder. Even in group therapy format CBT-SAD would be more expensive. (LOE = 1b)
Rohan KJ, Mahon JN, Evans M, et al. Randomized trial of cognitive-behavioral therapy versus light therapy for seasonal affective disorder: acute outcomes. Am J Psychiatry 2015;172:862-9.

4. Light therapy for bipolar depression

Clinical question: Is adjunctive bright light therapy beneficial for patients with bipolar depression?
Study design: Randomized controlled trial (double-blinded)
Allocation: Concealed
Funding source: Government
Setting: Outpatient (specialty)
Synopsis: The authors of this randomized controlled trial enrolled 46 adults aged 18 years to 75 years to assess whether adjunctive treatment with bright light therapy at midday improves remission and depression scores. Patients were included if they had a current episode of depression based on score of at least 20 on the Structured Interview Guide for the Hamilton Depression Rating Scale with Atypical Depression Supplement (SIGH-ADS), and no hypomania or mixed symptoms. Eligible patients received antimanic medication for at least 4 weeks prior to the active study period and could also receive antidepressants (78%) or sleep aid medications, if applicable. Patients were not eligible if they had a history of manic symptoms within the prior 6 months, rapid cycling within the past year, active suicidal ideation, psychosis, obsessive-compulsive disorder, uncontrolled thyroid disease, substance use disorder within the past 6 months, a positive urine drug screening result, eye diseases, or treatment with photosensitizing drugs. Patients were randomized to receive broad spectrum fluorescent bright light therapy or placebo dim red light therapy. Patients were masked to the kind of light used in the light box provided and agreed not to search for information about their light box therapy. Light therapy was initiated with a 15-minute session daily between noon and 2:30 PM, increasing by 15 minutes per week to 60 minutes daily by week 4. Titration was conditional on having manageable side effects using the Systematic Assessment for Treatment Emergent Effects scale. Use of the light sources was time-stamped and patients also logged light therapy sessions in a journal. The active treatment group had a higher remission rate of 8 or less on SIGH-ADS, (68% vs 22%; odds ratio 7.5; 95% CI 1.8 - 31.3; P = .003) and a lower mean depression score at the end of the study (9.2 vs 14.9 on SIGH-ADS; P = .03). No hypomania or mood polarity switches occurred. The active treatment group also had higher global functioning (Global Assessment of Function [GAF] score 75 vs 68; P = .03). The study was ended when funding ended, resulting in a smaller-than-planned sample size and wide confidence intervals. It could be questioned whether the statistically significant improvements in the SIGH-ADS and GAF were clinically meaningful
Bottom line: In adult patients with bipolar I or II depression, without hypomania or mania, adjunctive treatment with bright light therapy at midday resulted in a significantly higher remission rate and lower depression scores at study end. No episodes of mania were observed, but the study was not powered to evaluate that outcome. This was a relatively small study with wide confidence intervals; further studies are needed. (LOE = 1b-)
Sit DK, McGowan J, Wiltrout C, et al. Adjunctive bright light therapy for bipolar depression: A randomized double-blind placebo-controlled trial. Am J Psychiatry 2018;175(2):131-139.

5. Escitalopram reduces risk of adverse cardiac events in adults with depression and acute coronary syndrome

Clinical question: Does the treatment of depression with escitalopram in adults with recent acute coronary syndrome reduce the risk of subsequent major adverse cardiac events?
Study design: Randomized controlled trial (double-blinded) **Funding source:** Government
Allocation: Uncertain **Setting:** Outpatient (specialty)
Synopsis. Escitalopram is effective in reducing depressive symptoms in clinically depressed adults following acute coronary syndrome, but it is uncertain if treatment also lowers the risk of subsequent MACE. These investigators analyzed long-term follow-up data from a 24-week randomized trial started in 2007 that evaluated the effect of escitalopram for treating depression in adults following acute coronary syndrome. Telephone contact with patients or their family members and information obtained from hospital records and death registries resulted in complete follow-up for all 300 participants for a median of 8.1 years. An independent endpoint committee masked to treatment group assignments assessed all outcomes. Using intention-to-treat analysis, MACE incidence (a composite of all-cause mortality, recurrent myocardial infarction, and percutaneous coronary intervention) occurred significantly less in the escitalopram group than in the placebo group (40.9% vs 53.6%, respectively; number needed to treat = 7.9; 95% CI 4.2 - 71.0). The difference was not significant, however, in the subgroup of patients with impaired left ventricular ejection fraction (< 55%) at baseline. Patients with a significant remission of their depression also had a significantly less risk of MACE than those without remission of their depression.
Bottom line. Treatment of depression with escitalopram in adults with recent acute coronary syndrome is significantly superior to placebo in reducing depressive symptoms. It also significantly reduces the risk of subsequent major adverse cardiac events (MACE). (LOE = 1b-)
Kim JM, Stewart R, Lee YS, et al. Effect of escitalopram vs placebo treatment for depression on long-term cardiac outcomes in patients with acute coronary syndrome. A randomized clinical trial. JAMA 2018;320(4):350-357.

6. Prevalence of unrecognized bipolar disorder in primary care patients

Clinical Question: What is the prevalence of bipolar disorder among primary care patients prescribed antidepressants?
Study Design: Observational
Funding Source:
Setting: Primary care practices in UK
Synopsis: Aim: To determine the prevalence of unrecognised bipolar disorder among those prescribed antidepressants for depressive or anxiety disorder in UK primary care; whether those with unrecognised bipolar disorder have more severe depression than those who do not; and the accuracy of a screening questionnaire for bipolar disorder, the Mood Disorder Questionnaire (MDQ), in this setting.
Method: Participants were recruited using primary care databases, interviewed using a diagnostic interview, and completed the screening questionnaire and rating scales of symptoms and quality of life. Results: The prevalence of unrecognised bipolar disorder was 7.3%. Adjusting for differences between the sample and a national database gives a prevalence of 10.0%. Those with unrecognised bipolar disorder were younger and had greater lifetime depression. The predictive value of the MDQ was poor.
Bottom Line: Among people aged 16-40 years prescribed antidepressants in primary care for depression or anxiety, there is a substantial proportion with unrecognised bipolar disorder. When seeing patients with depression or anxiety disorder, particularly when they are young or not doing well, clinicians should review the life history for evidence of unrecognised bipolar disorder. Some clinicians might find the MDQ to be a useful supplement to non-standardised questioning.
Hughes T, Cardno A, West R, Marino-Francis F, Featherstone I, Rolling K, Locker A, McLintock K, House A. Unrecognised bipolar disorder among UK primary care patients prescribed ntidepressants: an observational study. Br J Gen Pract. 2016 Feb;66(643):e71-7. doi: 10.3399/bjgp16X683437. Epub 2016 Jan 6.

Social Anxiety Disorder

7. Diagnosis & treatment of social anxiety disorder

Clinical question: How should possible social anxiety disorder be diagnosed and treated?
Study design: Practice guideline
Funding source: Government
Setting: Various (guideline)
Synopsis: According to the authors of this guideline, social anxiety disorder has a lifetime prevalence of 6.7% and is characterized as severely impairing daily functioning by impeding the formation of relationships, reducing quality of life, and negatively affecting work and school performance. These guidelines suggest that physicians: (1) Perform a comprehensive assessment after identification of possible social anxiety disorder in children and adults (expert opinion). (2) Offer individual CBT specifically developed to treat social anxiety disorder as first-line treatment for adults. Do not offer group therapy (based on a systematic review). For children, consider individual or group CBT; do not routinely offer drug therapy (based on a systematic review). (3) Use supported self-help as second-line treatment. Consider drug therapy with an SSRI only after pressing patients to try CBT first (expert opinion). (4) Use short-term psychodynamic psychotherapy specifically developed for social anxiety disorder as third-line treatment (based on a systematic review). The full guideline can be found at: http://www.nice.org.uk/CG159
Bottom line: Patients with possible social anxiety should receive a complete assessment before a diagnosis is assigned. Cognitive behavioral therapy (CBT) is first-line treatment for children, adolescents, and adults with social anxiety disorder. Treatment with selective serotonin reuptake inhibitors (SSRIs) should be reserved for patients who decline CBT and cannot be talked into it. (LOE = 5)

Pilling S, Mayo-Wilson E, Mavranezouli I, et al, for the Guideline Development Group. Recognition, assessment and treatment of social anxiety disorder: summary of NICE guidance. BMJ 2013;346:f254.

8. Cognitive behavioral therapy best for social anxiety disorder

BACKGROUND: Social anxiety disorder-a chronic and naturally unremitting disease that causes substantial impairment-can be treated with pharmacological, psychological, and self-help interventions. We aimed to compare these interventions and to identify which are most effective for the acute treatment of social anxiety disorder in adults.
METHODS: We did a systematic review and network meta-analysis of interventions for adults with social anxiety disorder, identified from published and unpublished sources between 1988 and Sept 13, 2013. We analysed interventions by class and individually. Outcomes were validated measures of social anxiety, reported as standardised mean differences (SMDs) compared with a waitlist reference. This study is registered with PROSPERO, number CRD42012003146.
FINDINGS: We included 101 trials (13 164 participants) of 41 interventions or control conditions (17 classes) in the analyses. Classes of pharmacological interventions that had greater effects on outcomes compared with waitlist were monoamine oxidase inhibitors (SMD -1·01, 95% credible interval [CrI] -1·56 to -0·45), benzodiazepines (-0·96, -1·56 to -0·36), selective serotonin-reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs; -0·91, -1·23 to -0·60), and anticonvulsants (-0·81, -1·36 to -0·28). Compared with waitlist, efficacious classes of psychological interventions were individual cognitive-behavioural therapy (CBT; SMD -1·19, 95% CrI -1·56 to -0·81), group CBT (-0·92, -1·33 to -0·51), exposure and social skills (-0·86, -1·42 to -0·29), self-help with support (-0·86, -1·36 to -0·36), self-help without support (-0·75, -1·25 to -0·26), and psychodynamic psychotherapy (-0·62, -0·93 to -0·31). Individual CBT compared with psychological placebo (SMD -0·56, 95% CrI -1·00 to -0·11), and SSRIs and SNRIs compared with pill placebo (-0·44, -0·67 to -0·22) were the only classes of interventions that had greater effects on outcomes than appropriate placebo. Individual CBT also had a greater effect than psychodynamic psychotherapy (SMD -0·56, 95% CrI -1·03 to -0·11) and interpersonal psychotherapy, mindfulness, and supportive therapy (-0·82, -1·41 to -0·24).
INTERPRETATION: Individual CBT (which other studies have shown to have a lower risk of side-effects than pharmacotherapy) is associated with large effect sizes. Thus, it should be regarded as the best intervention for the initial treatment of social anxiety disorder. For individuals who decline psychological intervention, SSRIs show the most consistent evidence of benefit.
Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, Pilling S. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2014 Oct;1(5):368-76.

9. Pharmacotherapy of Social Anxiety Disorder

Background: Recognition is growing that social anxiety disorder (SAnD) is a chronic and disabling disorder, and data from early trials demonstrate that medication may be effective in its treatment. This systematic review is an update of an earlier review of pharmacotherapy of SAnD.
Objectives: To assess the effects of pharmacotherapy for social anxiety disorder in adults and identify which factors (methodological or clinical) predict response to treatment.
Search methods: We searched the Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR-Studies and CCMDCTR-References) to 17 August 2015. The CCMDCTR contains reports of relevant RCTs from MEDLINE (1950-), Embase (1974-), PsycINFO (1967-) and CENTRAL (all years). We scanned the reference lists of articles for additional studies. We updated the search in August 2017 and placed additional studies in Awaiting Classification, these will be incorporated in the next version of the review, as appropriate.
Selection criteria: We restricted studies to randomised controlled trials (RCTs) of pharmacotherapy versus placebo in the treatment of SAnD in adults.
Data collection and analysis: Two authors (TW and JI) assessed trials for eligibility and inclusion for this review update. We extracted descriptive, methodological and outcome information from each trial, contacting investigators for missing information where necessary. We calculated summary statistics for continuous and dichotomous variables (if provided) and undertook subgroup and sensitivity analyses.
Main results: We included 66 RCTs in the review (> 24 weeks; 11,597 participants; age range 18 to 70 years) and 63 in the meta-analysis. For the primary outcome of treatment response, we found very low-quality evidence of treatment response for selective serotonin reuptake inhibitors (SSRIs) compared with placebo (number of studies (k) = 24, risk ratio (RR) 1.65; 95% confidence interval (CI) 1.48 to 1.85, N = 4984). On this outcome there was also evidence of benefit for monoamine oxidase inhibitors (MAOIs) (k = 4, RR 2.36; 95% CI 1.48 to 3.75, N = 235), reversible inhibitors of monoamine oxidase A (RIMAs) (k = 8, RR 1.83; 95% CI 1.32 to 2.55, N = 1270), and the benzodiazepines (k = 2, RR 4.03; 95% CI 2.45 to 6.65, N = 132), although the evidence was low quality. We also found clinical response for the anticonvulsants with gamma-amino butyric acid (GABA) analogues (k = 3, RR 1.60; 95% CI 1.16 to 2.20, N = 532; moderate-quality evidence). The SSRIs were the only medication proving effective in reducing relapse based on moderate-quality evidence. We assessed tolerability of SSRIs and the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine on the basis of treatment withdrawal; this was higher for medication than placebo (SSRIs: k = 24, RR 2.59; 95% CI 1.97 to 3.39, N = 5131, low-quality evidence; venlafaxine: k = 4, RR 3.23; 95% CI 2.15 to 4.86, N = 1213, moderate-quality evidence), but there were low absolute rates of withdrawal for both these medications classes compared to placebo. We did not find evidence of a benefit for the rest of the medications compared to placebo.
For the secondary outcome of SAnD symptom severity, there was benefit for the SSRIs, the SNRI venlafaxine, MAOIs, RIMAs, benzodiazepines, the antipsychotic olanzapine, and the noradrenergic and specific serotonergic antidepressant (NaSSA) atomoxetine in the reduction of SAnD symptoms, but most of the evidence was of very low quality. Treatment with SSRIs and RIMAs was also associated with a reduction in depression symptoms. The SSRIs were the only medication class that demonstrated evidence of reduction in disability across a number of domains.

We observed a response to long-term treatment with medication for the SSRIs (low-quality evidence), for the MAOIs (very low-quality evidence) and for the RIMAs (moderate-quality evidence).
Authors' conclusions: We found evidence of treatment efficacy for the SSRIs, but it is based on very low- to moderate-quality evidence. Tolerability of SSRIs was lower than placebo, but absolute withdrawal rates were low. While a small number of trials did report treatment efficacy for benzodiazepines, anticonvulsants, MAOIs, and RIMAs, readers should consider this finding in the context of potential for abuse or unfavorable side effects.
Williams T, Hattingh CJ, Kariuki CM, Tromp SA, van Balkom AJ, Ipser JC, Stein DJ. Pharmacotherapy for social anxiety disorder (SAnD). Cochrane Database Syst Rev. 2017 Oct 19;10:CD001206.

Other Anxiety Disorders

10. Pharmacotherapy for panic disorder

BACKGROUND: Panic disorder is characterised by repeated, unexpected panic attacks, which represent a discrete period of fear or anxiety that has a rapid onset, reaches a peak within 10 minutes, and in which at least four of 13 characteristic symptoms are experienced, including racing heart, chest pain, sweating, shaking, dizziness, flushing, stomach churning, faintness and breathlessness. It is common in the general population with a lifetime prevalence of 1% to 4%. Amongst pharmacological agents, the National Institute for Health and Care Excellence (NICE) and the British Association for Psychopharmacology consider antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs), as the first-line treatment for panic disorder, due to their more favourable adverse effect profile over monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).
OBJECTIVES: To assess the effects of antidepressants for panic disorder in adults. 1. to determine the efficacy of antidepressants in alleviating symptoms of panic disorder, with or without agoraphobia, in comparison to placebo; 2. to review the acceptability of antidepressants in panic disorder, with or without agoraphobia, in comparison with placebo; and 3. to investigate the adverse effects of antidepressants in panic disorder, with or without agoraphobia, including the general prevalence of adverse effects, compared to placebo.
SEARCH METHODS: We searched the Cochrane Common Mental Disorders' (CCMD) Specialised Register, and CENTRAL, MEDLINE, EMBASE and PsycINFO up to May 2017. We hand-searched reference lists of relevant papers and previous systematic reviews.
SELECTION CRITERIA: All double-blind, randomised, controlled trials (RCTs) allocating adults with panic disorder to antidepressants or placebo.
DATA COLLECTION AND ANALYSIS: Two review authors independently checked eligibility and extracted data using a standard form. We entered data into Review Manager 5 using a double-check procedure. Information extracted included study characteristics, participant characteristics, intervention details and settings. Primary outcomes included failure to respond, measured by a range of response scales, and treatment acceptability, measured by total number of dropouts for any reason. Secondary outcomes included failure to remit, panic symptom scales, frequency of panic attacks, agoraphobia, general anxiety, depression, social functioning, quality of life and patient satisfaction, measured by various scales as defined in individual studies. We used GRADE to assess the quality of the evidence for each outcome.
MAIN RESULTS: Forty-one unique RCTs including 9377 participants overall, of whom we included 8252 in the 49 placebo-controlled arms of interest (antidepressant as monotherapy and placebo alone) in this review. The majority of studies were of moderate to low quality due to inconsistency, imprecision and unclear risk of selection and performance bias. We found low-quality evidence that revealed a benefit for antidepressants as a group in comparison with placebo in terms of efficacy measured as failure to respond (risk ratio (RR) 0.72, 95% confidence interval (CI) 0.66 to 0.79; participants = 6500; studies = 30). The magnitude of effect corresponds to a number needed to treat for an additional beneficial outcome (NNTB) of 7 (95% CI 6 to 9): that means seven people would need to be treated with antidepressants in order for one to benefit. We observed the same finding when classes of antidepressants were compared with placebo. Moderate-quality evidence suggested a benefit for antidepressants compared to placebo when looking at number of dropouts due to any cause (RR 0.88, 95% CI 0.81 to 0.97; participants = 7850; studies = 30). The magnitude of effect corresponds to a NNTB of 27 (95% CI 17 to 105); treating 27 people will result in one person fewer dropping out. Considering antidepressant classes, TCAs showed a benefit over placebo, while for SSRIs and serotonin-norepinephrine reuptake inhibitor (SNRIs) we observed no difference. When looking at dropouts due to adverse effects, which can be considered as a measure of tolerability, we found moderate-quality evidence showing that antidepressants as a whole are less well tolerated than placebo. In particular, TCAs and SSRIs produced more dropouts due to adverse effects in comparison with placebo, while the confidence interval for SNRI, noradrenergic reuptake inhibitors (NRI) and other antidepressants were wide and included the possibility of no difference.
AUTHORS' CONCLUSIONS: Based on these results, antidepressants may be more effective than placebo in treating panic disorder. Efficacy can be quantified as a NNTB of 7, implying that seven people need to be treated with antidepressants in order for one to benefit. Antidepressants may also have benefit in comparison with placebo in terms of number of dropouts, but a less favorable profile in terms of dropout due to adverse effects. However, the tolerability profile varied between different classes of antidepressants. Limitations in results include funding of some studies by pharmaceutical companies, and only assessing short-term outcomes.
Bighelli I, Castellazzi M, Cipriani A, Girlanda F, Guaiana G, Koesters M, Turrini G, Furukawa TA, Barbui C. Antidepressants versus placebo for panic disorder in adults. Cochrane Database Syst Rev. 2018 Apr 5;4:CD010676.

11. CBT and SSRIs effective for childhood anxiety disorders

IMPORTANCE: Childhood anxiety is common. Multiple treatment options are available, but existing guidelines provide inconsistent advice on which treatment to use.
OBJECTIVES: To evaluate the comparative effectiveness and adverse events of cognitive behavioral therapy (CBT)

and pharmacotherapy for childhood anxiety disorders.
DATA SOURCES: We searched MEDLINE, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and SciVerse Scopus from database inception through February 1, 2017.
STUDY SELECTION: Randomized and nonrandomized comparative studies that enrolled children and adolescents with confirmed diagnoses of panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder, or separation anxiety and who received CBT, pharmacotherapy, or the combination.
DATA EXTRACTION AND SYNTHESIS: Independent reviewers selected studies and extracted data. Random-effects meta-analysis was used to pool data.
MAIN OUTCOMES AND MEASURES: Primary anxiety symptoms (measured by child, parent, or clinician), remission, response, and adverse events.
RESULTS: A total of 7719 patients were included from 115 studies. Of these, 4290 (55.6%) were female, and the mean (range) age was 9.2 (5.4-16.1) years. Compared with pill placebo, selective serotonin reuptake inhibitors (SSRIs) significantly reduced primary anxiety symptoms and increased remission (relative risk, 2.04; 95% CI, 1.37-3.04) and response (relative risk, 1.96; 95% CI, 1.60-2.40). Serotonin-norepinephrine reuptake inhibitors (SNRIs) significantly reduced clinician-reported primary anxiety symptoms. Benzodiazepines and tricyclics were not found to significantly reduce anxiety symptoms. When CBT was compared with wait-listing/no treatment, CBT significantly improved primary anxiety symptoms, remission, and response. Cognitive behavioral therapy reduced primary anxiety symptoms more than fluoxetine and improved remission more than sertraline. The combination of sertraline and CBT significantly reduced clinician-reported primary anxiety symptoms and response more than either treatment alone. Head-to-head comparisons were sparse, and network meta-analysis estimates were imprecise. Adverse events were common with medications but not with CBT and were not severe. Studies were too small or too short to assess suicidality with SSRIs or SNRIs. One trial showed a statistically nonsignificant increase in suicidal ideation with venlafaxine. Cognitive behavioral therapy was associated with fewer dropouts than pill placebo or medications.
CONCLUSIONS AND RELEVANCE: Evidence supports the effectiveness of CBT and SSRIs for reducing childhood anxiety symptoms. Serotonin-norepinephrine reuptake inhibitors also appear to be effective based on less consistent evidence. Head-to-head comparisons between various medications and comparisons with CBT represent a need for research in the field.
Wang Z, Whiteside SPH Sim L, Farah W, Morrow AS, Alsawas M, Barrionuevo P, Tello M, Asi N, et. al. Comparative Effectiveness and Safety of Cognitive Behavioral Therapy and Pharmacotherapy for Childhood Anxiety Disorders: A Systematic Review and Meta-analysis. JAMA Pediatr. 2017 Nov 1;171(11):1049-1056.

12. Higher doses of SSRIs but not SNRIs are more effective

BACKGROUND: We aimed to examine the efficacy of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) for anxiety disorders examining overall symptom improvement, likelihood of treatment response, time course of treatment response, individual pharmacological agent, diagnostic indication dose, and tolerability.
METHODS: We searched PubMed and Cochrane Central Register of Controlled Trials. We included randomized placebo-controlled clinical trials of SSRIs/SNRIs in adult patients with anxiety disorders that provided data at three or more time points. Extracted data included trial duration, weekly/biweekly anxiety scores for 12 weeks.
RESULTS: Meta-analysis included 57 trials (N = 16,056). A linear mixed model analysis based on weekly outcome data suggested that for SNRI a logarithmic model offered the best fit compared to placebo (indicating the greatest incremental improvement from baseline occurred early in treatment); whereas for SSRI a linear model provided the best fit (indicating a similar improvement over the duration of the acute treatment phase). There were no significant differences in efficacy between pharmacological agents within each class or when comparing SSRIs to SNRIs. The greatest treatment benefits were observed for social anxiety disorder for both medication classes. Higher doses of SSRIs, but not SNRIs, were associated with significantly greater symptom improvement and likelihood of treatment response. For both medical classes, higher doses were associated with an increased likelihood of dropout due to side effects.
CONCLUSIONS: SSRIs and SNRIs are effective in treating anxiety disorders. Higher doses of SSRIs within the therapeutic range are associated with greater treatment benefit, whereas higher doses of SNRIs are not.
Jakubovski E, Johnson JA, Nasir M, Müller-Vahl K, Bloch MH. Systematic review and meta-analysis: Dose-response curve of SSRIs and SNRIs in anxiety disorders. Depress Anxiety. 2018 Nov 26. doi: 10.1002/da.22854. [Epub ahead of print]

13. Is the effectiveness of SSRIs due largely to verbal suggestion (placebo)?

BACKGROUND: Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed for depression and anxiety, but their efficacy relative to placebo has been questioned. We aimed to test how manipulation of verbally induced expectancies, central for placebo, influences SSRI treatment outcome and brain activity in patients with social anxiety disorder (SAD).
METHODS: We did a randomized clinical trial, within an academic medical center (Uppsala, Sweden), of individuals fulfilling the DSM-IV criteria for SAD, recruited through media advertising. Participants were 18years or older and randomized in blocks, through a computer-generated sequence by an independent party, to nine weeks of overt or covert treatment with escitalopram (20mg daily). The overt group received correct treatment information whereas the covert group was treated deceptively with the SSRI described, by the psychiatrist, as active placebo. The treating psychiatrist was necessarily unmasked while the research staff was masked from intervention assignment. Treatment efficacy was assessed primarily with the self-rated Liebowitz Social Anxiety Scale (LSAS-SR), administered at week 0, 1, 3, 6 and 9, also yielding a dichotomous estimate of responder status (clinically significant improvement). Before and at the last week of treatment, brain activity during an emotional face-matching task was assessed with functional magnetic resonance imaging (fMRI) and during fMRI sessions, anticipatory speech anxiety was also assessed with the Spielberger State-Trait Anxiety Inventory - State version (STAI-S). Analyses included all randomized patients with outcome data at posttreatment. This

study is registered at ISRCTN, number 98890605.
FINDINGS: Between March 17th 2014 and May 22nd 2015, 47 patients were recruited. One patient in the covert group dropped out after a few days of treatment and did not provide fMRI data, leaving 46 patients with complete outcome data. After nine weeks of treatment, overt (n=24) as compared to covert (n=22) SSRI administration yielded significantly better outcome on the LSAS-SR (adjusted difference 21.17, 95% CI 10.69-31.65, p<0.0001) with more than three times higher response rate (50% vs. 14%; $\chi^2(1)=6.91$, p=0.009) and twice the effect size (d=2.24 vs. d=1.13) from pre-to posttreatment. There was no significant between-group difference on anticipatory speech anxiety (STAI-S), both groups improving with treatment. No serious adverse reactions were recorded. On fMRI outcomes, there was suggestive evidence for a differential neural response to treatment between groups in the posterior cingulate, superior temporal and inferior frontal gyri (all z thresholds exceeding 3.68, p≤0.001). Reduced social anxiety with treatment correlated significantly with enhanced posterior cingulate (z threshold 3.24, p=0.0006) and attenuated amygdala (z threshold 2.70, p=0.003) activity.
INTERPRETATION: The clinical and neural effects of escitalopram were markedly influenced by verbal suggestions. This points to a pronounced placebo component in SSRI-treatment of SAD and favors a biopsychosocial over a biomedical explanatory model for SSRI efficacy.
Faria V, Gingnell M, Hoppe JM, Hjorth O, Alaie I, Frick A. Do You Believe It? Verbal Suggestions Influence the Clinical and Neural Effects of Escitalopram in Social Anxiety Disorder: A Randomized Trial. EBioMedicine. 2017 Oct;24:179-188.

Novel treatments for mental health disorders

14. Eye movement desensitization and reprocessing (EMDR) better than CBT for PTSD

Background. Post-traumatic stress disorder (PTSD) is prevalent in children, adolescents and adults. It can occur alone or in comorbidity with other disorders. A broad range of psychotherapies such as cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) have been developed for the treatment of PTSD. Aim Through quantitative meta-analysis, we aimed to compare the efficacy of CBT and EMDR: (i) relieving the post-traumatic symptoms, and (ii) alleviating anxiety and depression, in patients with PTSD.
Methods. We systematically searched EMBASE, Medline and Cochrane central register of controlled trials (CENTRAL) for articles published between 1999 and December 2017. Randomized clinical trials (RCTs) that compare CBT and EMDR in PTSD patients were included for quantitative meta-analysis using RevMan Version 5.
Results. Fourteen studies out of 714 were finally eligible. Meta-analysis of 11 studies (n = 547) showed that EMDR is better than CBT in reducing post-traumatic symptoms [SDM (95% CI) = -0.43 (-0.73 - -0.12), p = 0.006]. However, meta-analysis of four studies (n = 186) at three-month follow-up revealed no statistically significant difference [SDM (95% CI) = -0.21 (-0.50 - 0.08), p = 0.15]. The EMDR was also better than CBT in reducing anxiety [SDM (95% CI) = -0.71 (-1.21 - -0.21), p = 0.005]. Unfortunately, there was no difference between CBT and EMDR in reducing depression [SDM (95% CI) = -0.21 (-0.44 - 0.02), p = 0.08].
Conclusion. The results of this meta-analysis suggested that EMDR is better than CBT in reducing post-traumatic symptoms and anxiety. However, there was no difference reported in reducing depression. Large population randomized trials with longer follow-up are recommended to build conclusive evidence.
Khan AM, Dar S, Ahmed R, Bachu R, Adnan M, Kotapati VP. Cognitive Behavioral Therapy versus Eye Movement Desensitization and Reprocessing in Patients with Post-traumatic Stress Disorder: Systematic Review and Meta-analysis of Randomized Clinical Trials. Cureus. 2018 Sep 4;10(9):e3250.

15. Mindfulness interventions somewhat effective for symptoms of bipolar disorder

Background: Despite the increasing number of studies examining the effects of mindfulness interventions on symptoms associated with Bipolar Disorder (BD), the effectiveness of this type of interventions remains unclear. The aim of the present systematic review was to (i) critically review all available evidence on Mindfulness Based Cognitive Therapy (MBCT) as a form of intervention for BD; (ii) discuss clinical implications of MBCT in treating patients with BD; and (iii) provide a direction for future research. The review presents findings from 13 studies (N = 429) that fulfilled the following selection criteria: (i) included BD patients; (ii) presented results separately for BD patients and control groups (where a control group was available); (iii) implemented MBCT intervention; (iv) were published in English; (v) were published in a peer reviewed journal; and (vi) reported results for adult participants.
Results: Although derived from a relatively small number of studies, results from the present review suggest that MBCT is a promising treatment in BD in conjunction with pharmacotherapy. MBCT in BD is associated with improvements in cognitive functioning and emotional regulation, reduction in symptoms of anxiety depression and mania symptoms (when participants had residual manic symptoms prior to MBCT). These, treatment gains were maintained at 12 month follow up when mindfulness was practiced for at least 3 days per week or booster sessions were included. Additionally, the present review outlined some limitations of the current literature on MBCT interventions in BD, including small study sample sizes, lack of active control groups and idiosyncratic modifications to the MBCT intervention across studies. Suggestions for future research included focusing on factors underlying treatment adherence and understanding possible adverse effects of MBCT, which could be of crucial clinical importance.
Bojic S, Becerra R. Mindfulness-Based Treatment for Bipolar Disorder: A Systematic Review of the Literature. Eur J Psychol. 2017 Aug 31;13(3):573-598.

16. Internet-based mindfulness interventions reduce symptoms of anxiety and depression

BACKGROUND: Web-based mindfulness interventions are increasingly delivered through the internet to treat mental health conditions.
OBJECTIVE: The objective of this study was to determine the effectiveness of web-based mindfulness interventions in clinical mental

health populations. Secondary aims were to explore the impact of study variables on the effectiveness of web-based mindfulness interventions.
METHODS: We performed a systematic review and meta-analysis of studies investigating the effects of web-based mindfulness interventions on clinical populations.
RESULTS: The search strategy yielded 12 eligible studies. Web-based mindfulness interventions were effective in reducing depression in the total clinical sample (n=656 g=-0.609, P=.004) and in the anxiety disorder subgroup (n=313, g=-0.651, P<.001), but not in the depression disorder subgroup (n=251, P=.18). Similarly, web-based mindfulness interventions significantly reduced anxiety in the total clinical sample (n=756, g=-0.433, P=.004) and the anxiety disorder subgroup (n=413, g=-0.719, P<.001), but not in the depression disorder group (n=251, g=-0.213, P=.28). Finally, web-based mindfulness interventions improved quality of life and functioning in the total sample (n=591, g=0.362, P=.02) in the anxiety disorder subgroup (n=370, g=0.550, P=.02) and mindfulness skills in the total clinical sample (n=251, g=0.724, P<.001).
CONCLUSIONS: Results support the effectiveness of web-based mindfulness interventions in reducing depression and anxiety and in enhancing quality of life and mindfulness skills, particularly in those with clinical anxiety. Results should be interpreted with caution given the high heterogeneity of web-based mindfulness interventions and the low number of studies included.
Sevilla-Llewellyn-Jones J, Santesteban-Echarri O, Pryor I, McGorry P, Alvarez-Jimenez M. Web-Based Mindfulness Interventions for Mental Health Treatment: Systematic Review and Meta-Analysis. JMIR Ment Health. 2018 Sep 25;5(3):e10278.

17. Therapist assisted Internet-based CBT effective for obsessive-compulsive disorder

BACKGROUND: Obsessive-compulsive disorder (OCD) is a highly disabling psychological disorder with a chronic course if left untreated. Cognitive behavioral therapy (CBT) has been shown to be an effective treatment, but access to face-to-face CBT is not always possible. Internet-based CBT (iCBT) has become an increasingly viable option. However, no study has compared iCBT to an analogous control condition using a randomized controlled trial (RCT).
OBJECTIVE: A 2-armed RCT was used to compare a therapist-assisted 12-module iCBT to an analogous active attention control condition (therapist-assisted internet-based standard progressive relaxation training, iPRT) in adult OCD. This paper reports pre-post findings for OCD symptom severity.
METHOD: In total, 179 participants (117 females, 65.7%) were randomized (stratified by gender) into iCBT or iPRT. The iCBT intervention included psychoeducation, mood and behavioral management, exposure and response prevention (ERP), cognitive therapy, and relapse prevention; the iPRT intervention included psychoeducation and relaxation techniques as a way of managing OCD-related anxiety but did not incorporate ERP or other CBT elements. Both treatments included audiovisual content, case stories, demonstrations of techniques, downloadable audio content and worksheets, and expert commentary. All participants received 1 weekly email, with a maximum 15-minute preparation time per client from a remote therapist trained in e-therapy. Emails aimed to monitor progress, provide support and encouragement, and assist in individualizing the treatment. Participants were assessed for baseline and posttreatment OCD severity with the telephone-administered clinician-rated Yale-Brown Obsessive-Compulsive Scale and other measures by assessors who were blinded to treatment allocation.
RESULTS: No pretreatment differences were found between the 2 conditions. Intention-to-treat analysis revealed significant pre-post improvements in OCD symptom severity for both conditions (P<.001). However, relative to iPRT, iCBT showed significantly greater symptom severity improvement (P=.001); Cohen d for iCBT was 1.05 (95% CI 0.72-1.37), whereas for iPRT it was 0.48 (95% CI 0.22-0.73). The iCBT condition was superior in regard to reliable improvement (25/51, 49% vs 16/55, 29%; P=.04) and clinically significant pre-post-treatment changes (17/51, 33% vs 6/55, 11%; P=.005). Those undertaking iCBT post completion of iPRT showed further significant symptom amelioration (P<.001), although the sequential treatment was no more efficacious than iCBT alone (P=.63).
CONCLUSION: This study is the first to compare a therapist-assisted iCBT program for OCD to an analogous active attention control condition using iPRT. Our findings demonstrate the large magnitude effect of iCBT for OCD; interestingly, iPRT was also moderately efficacious, albeit significantly less so than the iCBT intervention. The findings are compared to previous internet-based and face-to-face CBT treatment programs for OCD. Future directions for technology-enhanced programs for the treatment of OCD are outlined.
Kyrios M, Ahern C, Fassnacht DB, Nedeljkovic M, Moulding R, Meyer D. Therapist-Assisted Internet-Based Cognitive Behavioral Therapy Versus Progressive Relaxation in Obsessive-Compulsive Disorder: Randomized Controlled Trial. J Med Internet Res. 2018 Aug 8;20(8):e242.

Bottom lines

1. physical activity appears to reduce the risk of developing depression.

2. hormone replacement therapy reduces the risk of depression in peri-menopausal and early menopausal women.

3. light therapy reduces symptoms of seasonal affective disorder and bipolar depression.

4. Cognitive behavioral therapy is the preferred treatment for social anxiety disorder. SSRIs are also somewhat effective.

5. higher doses of SSRIs are more effective but higher doses of SNRIs are not more effective.

6. EMDR is effective in treating post-traumatic stress disorder (PTSD).

7. Mindfulness-based interventions in person or via the web can reduce symptoms of anxiety and depression, including bipolar disorder.

8. Therapist assisted Internet-based treatment of obsessive compulsive disorder is effective.

Understand

1. Emerging evidence on the harmful effects of sedentary time
2. The prevalence of cardiac arrests during triathlons
3. The variable effects of wearable technology
4. The effects of exercise on fall risk in the elderly
5. The effects of physical activity interventions during pregnancy
6. The effect of exercise and rehab on several common medical conditions
7. Ethical considerations of genetic testing for athletic pre-participation cardiac screening

Sedentary Time

#1 Physical activity & sedentary time are independently associated with all-cause mortality,

BACKGROUND: Some research suggests that being sedentary increases the risk of premature mortality even in people who engage in physical activity.
METHODS: This retrospective study coordinated at the University of Mississippi examined the joint effects of objectively measured sedentary time and physical activity in 5575 adults aged 20-85 (mean 46; 52% female) included in the 2003-2006 National Health and Nutrition Examination Survey. Participants were monitored for seven days with an accelerometer to determine sedentary time (activity count of 0-99/minute, with a threshold of above or below a median of 487 minutes/day) and moderate to vigorous physical activity (activity count 2020/minute or higher, with a cut-off of a median of 14 minutes/day). The study outcome was all-cause mortality.
RESULTS: During a median follow-up of 81 months, 511 participants died. Age-adjusted mortality rates were 5.3% overall, 2.4% for participants above the median activity level versus 6.9% for those below the median activity level, and 6.3% for those above the median sedentary level versus 3.8% for those below the median sedentary level. Each increase of one minute/day of physical activity reduced mortality risk (adjusted hazard ratio [HR], 0.98; 95% CI, 0.96-0.99; p=0.04), while each one minute/day increase in sedentary time increased mortality risk (HR 1.001; 95% CI, 1.0003-1.002; p=0.008). Sedentary time raised the mortality risk only in participants who exhibited physical activity below the median level (p<0.001), and not in those who exceeded the median activity level (p=0.32).
CONCLUSIONS: Physical activity and sedentary time appear to be independently associated with all-cause mortality, but being sedentary did not negate the benefits of regular exercise. 23 references
REFERENCE*: Loprinzi, P.D., et al. JOINT EFFECTS OF OBJECTIVELY-MEASURED SEDENTARY TIME AND PHYSICAL ACTIVITY ON ALL-CAUSE MORTALITY. Prev Med 90:47, September 2016*

#2 Prolonged uninterrupted bouts of sedentary time associated with all-cause mortality,

Background: Excessive sedentary time is ubiquitous in Western societies. Previous studies have relied on self-reporting to evaluate the total volume of sedentary time as a prognostic risk factor for mortality and have not examined whether the manner in which sedentary time is accrued (in short or long bouts) carries prognostic relevance.
Objective: To examine the association between objectively measured sedentary behavior (its total volume and accrual in prolonged, uninterrupted bouts) and all-cause mortality.
Design: Prospective cohort study.
Setting: Contiguous United States.
Participants: 7985 black and white adults aged 45 years or older.
Measurements: Sedentary time was measured using a hip-mounted accelerometer. Prolonged, uninterrupted sedentariness was expressed as mean sedentary bout length. Hazard ratios (HRs) were calculated comparing quartiles 2 through 4 to quartile 1 for each exposure (quartile cut points: 689.7, 746.5, and 799.4 min/d for total sedentary time; 7.7, 9.6, and 12.4 min/bout for sedentary bout duration) in models that included moderate to vigorous physical activity.
Results: Over a median follow-up of 4.0 years, 340 participants died. In multivariable-adjusted models, greater total sedentary time (HR, 1.22 [95% CI, 0.74 to 2.02]; HR, 1.61 [CI, 0.99 to 2.63]; and HR, 2.63 [CI, 1.60 to 4.30]; P for trend < 0.001) and longer sedentary bout duration (HR, 1.03 [CI, 0.67 to 1.60]; HR, 1.22 [CI, 0.80 to 1.85]; and HR, 1.96 [CI, 1.31 to 2.93]; P for trend < 0.001) were both associated with a higher risk for all-cause mortality. Evaluation of their joint association showed that participants classified as high for both sedentary characteristics (high sedentary time [≥12.5 h/d] and high bout duration [≥10 min/bout]) had the greatest risk for death.
Limitation: Participants may not be representative of the general U.S. population.
Conclusion: Both the total volume of sedentary time and its accrual in prolonged, uninterrupted bouts are associated with all-cause mortality, suggesting that physical activity guidelines should target reducing and interrupting sedentary time to reduce risk for death.
REFERENCE: *Diaz KM,et al. Patterns of Sedentary Behavior and Mortality in U.S. Middle-Aged and Older Adults: A National Cohort Study. Ann Intern Med. 2017 Oct 3;167(7):465-475.*

Cardiac Arrests During Triathlons

#3 Deaths and cardiac arrests during triathlons

Background: Reports of race-related triathlon fatalities have raised questions regarding athlete safety.
Objective: To describe death and cardiac arrest among triathlon participants.
Design: Case series.
Setting: United States.
Participants: Participants in U.S. triathlon races from 1985 to 2016.
Measurements: Data on deaths and cardiac arrests were assembled from such sources as the U.S. National Registry of Sudden Death in Athletes (which uses news media, Internet searches, LexisNexis archival databases, and news clipping services) and USA Triathlon (USAT) records. Incidence of death or cardiac arrest in USAT-sanctioned races from 2006 to 2016 was calculated.
Results: A total of 135 sudden deaths, resuscitated cardiac arrests, and trauma-related deaths were compiled; mean (±SE) age of victims was 46.7 ± 12.4 years, and 85% were male. Most sudden deaths and cardiac arrests occurred in the swim segment (n = 90); the others occurred during bicycling (n = 7), running (n = 15), and postrace recovery (n = 8). Fifteen trauma-related deaths occurred during the bike segment. Incidence of death or cardiac arrest among USAT participants (n = 4 776 443) was 1.74 per 100 000 (2.40 in men and 0.74 in women per 100 000; P < 0.001). In men, risk increased substantially with age and was much greater for those aged 60 years and older (18.6 per 100 000 participants). Death or cardiac arrest risk was similar for short, intermediate, and long races (1.61 vs. 1.41 vs. 1.92 per 100 000 participants). At autopsy, 27 of 61 decedents (44%) had clinically relevant cardiovascular abnormalities, most frequently atherosclerotic coronary disease or cardiomyopathy.
Limitations: Case identification may be incomplete and may underestimate events, particularly in the early study period. In addition, prerace medical history is unknown in most cases.
Conclusion: Deaths and cardiac arrests during the triathlon are not rare; most have occurred in middle-aged and older men. Most sudden deaths in triathletes happened during the swim segment, and clinically silent cardiovascular disease was present in an unexpected proportion of decedents.
Primary Funding Source: Minneapolis Heart Institute Foundation.
Reference: *Harris KM et al. Death and Cardiac Arrest in U.S. Triathlon Participants, 1985 to 2016: A Case Series. Ann Intern Med. 2017 Oct 17;167(8):529-535.*

Male, first-time participants had the highest mortality risk, and most arrests occurred during the swimming portion of events

#4 Cardiac arrests during triathlons

BACKGROUND: The incidence of sudden cardiac arrest during participation in sports activities remains unknown. Preparticipation screening programs aimed at preventing sudden cardiac arrest during sports activities are thought to be able to identify at-risk athletes; however, the efficacy of these programs remains controversial. We sought to identify all sudden cardiac arrests that occurred during participation in sports activities within a specific region of Canada and to determine their causes.
METHODS: In this retrospective study, we used the RescuEpistry cardiac arrest database (which contains records of every cardiac arrest attended by paramedics in the network region) to identify all out-of-hospital cardiac arrests that occurred from 2009 through 2014 in persons 12 to 45 years of age during participation in a sport. Cases were adjudicated as sudden cardiac arrest (i.e., having a cardiac cause) or as an event resulting from a noncardiac cause, on the basis of records from multiple sources, including ambulance call reports, autopsy reports, in-hospital data, and records of direct interviews with patients or family members.
RESULTS: Over the course of 18.5 million person-years of observation, 74 sudden cardiac arrests occurred during participation in a sport; of these, 16 occurred during competitive sports and 58 occurred during noncompetitive sports. The incidence of sudden cardiac arrest during competitive sports was 0.76 cases per 100,000 athlete-years, with 43.8% of the athletes surviving until they were discharged from the hospital. Among the competitive athletes, two deaths were attributed to hypertrophic cardiomyopathy and none to arrhythmogenic right ventricular cardiomyopathy. Three cases of sudden cardiac arrest that occurred during participation in competitive sports were determined to have been potentially identifiable if the athletes had undergone preparticipation screening.
CONCLUSIONS: In our study involving persons who had out-of-hospital cardiac arrest, the incidence of sudden cardiac arrest during participation in competitive sports was 0.76 cases per 100,000 athlete-years. The occurrence of
sudden cardiac arrest due to structural heart disease was uncommon during participation in competitive sports. (Funded by the National Heart, Lung, and Blood Institute and others.)
Reference: Landry CH et al. Sudden Cardiac Arrest during Participation in Competitive Sports. N Engl J Med. 2017 Nov 16;377(20):1943-1953.

Wearable Technology

#5 Adults show a small increase (10%) in steps when given pedometers

Clinical question: Is the use of a pedometer an effective way to increase activity in adults?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: These investigators recruited 1023 individuals from primary care practices who were at least 45 years of age (30% were aged 65 to 75 years). Although the enrollment criteria specified that they did not perform moderate to vigorous physical activity for at least 30 minutes, 5 days a week, the participants were fairly active people: At baseline, the average participant recorded 7479 steps

and spent 94 minutes a week in moderate to vigorous activity. Approximately 63% were women, 80% were white, fewer than 10% were smokers, 65% were overweight or obese, and most described themselves as being in good health. The participants were randomized (concealed allocation unknown) to continue to receive usual care, to receive a pedometer by mail, or to receive a pedometer by mail and have nurse-led consultations 3 times over the first 9 weeks of the study. The 2 pedometer groups also received a physical activity diary and a 12-week walking program. After 1 year, both intervention groups recorded an additional 642 to 677 steps as compared with the control group (P < .001) and an additional 33 to 35 minutes spent in moderate to vigorous physical activity. Weight loss, depression scores, and anxiety scores were similar across all 3 groups, including adverse effects.
Bottom line: In a group of adults who were already fairly active, giving them a pedometer increased their steps per day by an average 650 steps. As with a previous study in younger people (Jakicic JM, et al. JAMA 2016;316:1161-71), the use of the pedometer did not promote weight loss.
Harris T, Kerry SM, Limb ES. Effect of a primary care walking intervention with and without nurse support on physical activity levels in 45- to 75-year-olds: the pedometer and consultation evaluation (PACE-UP) cluster randomised clinical trial. PLoS Med 2017;14(1):e1002210.

#6 Wearable technology combined with lifestyle intervention = LESS weight loss

Clinical question: Compared with standard behavioral weight-loss programs, does a technology-enhanced weight-loss intervention, including a wearable device, result in greater long-term weight loss in adults?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (any)
Synopsis: Many commercial technologies, including wearable devices, are available to provide feedback on physical activity and diet. However, there are limited data on the long-term effectiveness of these technologies. These investigators identified adults, aged 18 to 35 years, with a body mass index (BMI) of 25.0 to 39.9. Eligible participants (N = 470) randomly received assignment (concealed) to either a standard behavioral weight-loss intervention group or the technology-enhanced weight-loss group. Both groups received behavioral weight loss education on diet and exercise for 6 months, and at 6 months both groups also received weekly telephone counseling sessions, weekly text message prompts, and access to study materials on a website. After 6 months, participants in the standard group initiated self-monitoring of diet and physical activity, while those in the technology-enhanced group began using a wearable device along with a web-based interface (FITCore; Body Media) to monitor physical activity and diet. Individuals who assessed outcomes remained masked to treatment group assignment. Complete follow-up occurred for 74.5% of participants at 24 months. Intention-to-treat analysis showed that participants in the enhanced-intervention group lost significantly less weight at 24 months that those in the standard-intervention group (mean loss = 3.5 kg; 95% CI 2.6 - 4.5 vs mean loss = 5.9 kg; 5.0 - 6.8; mean difference = 2.4 kg; 1.0 - 3.7). The percent weight loss was also significantly less in the enhanced-intervention group than in the standard-intervention group (3.6% vs 6.4% at 24 months). No significant group differences occurred for fat mass, lean mass, percent body fat, bone mineral density, or cardiorespiratory fitness.
Bottom line: This study found that a weight-loss program for adults, aged 18 to 35 years, that included technology-enhanced weight-loss interventions (a wearable device and a web-based interface) resulted in LESS weight loss than standard weight-loss education focusing on dietary changes and increased physical activity. Here's how I think it went down: Should I eat that yummy piece of chocolate cake? Those in the standard group said "Nope" (because they figured they shouldn't). Those in the technology-enhanced group, however, said, "Let me look at my device. I've walked a lot today, so I'm eating the cake!"
Jakicic JM, Davis KK, Rogers RJ, et al. Effect of wearable technology combined with a lifestyle intervention on long-term weight loss. The IDEA randomized clinical trial. JAMA 2016;316(11):1161-1171.

Exercise / Rehab for medical conditions

#7 In stable CHD, more exercise associated with lower mortality

BACKGROUND: Recommendations for physical activity in patients with stable coronary heart disease (CHD) are based on modest evidence.
OBJECTIVES: The authors analyzed the association between self-reported exercise and mortality in patients with stable CHD.
METHODS: A total of 15,486 patients from 39 countries with stable CHD who participated in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) study completed questions at baseline on hours spent each week taking mild, moderate, and vigorous exercise. Associations between the volume of habitual exercise in metabolic equivalents of task hours/week and adverse outcomes during a median follow-up of 3.7 years were evaluated.
RESULTS: A graded decrease in mortality occurred with increased habitual exercise that was steeper at lower compared with higher exercise levels. Doubling exercise volume was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.79 to 0.85; adjusting for covariates, HR: 0.90; 95% CI: 0.87 to 0.93). These associations were similar for cardiovascular mortality (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96), but myocardial infarction and stroke were not associated with exercise volume after adjusting for covariates. The association between decrease in mortality and greater physical activity was stronger in the subgroup of patients at higher risk estimated by the ABC-CHD (Age, Biomarkers, Clinical-Coronary Heart Disease) risk score (p for interaction = 0.0007).
CONCLUSIONS: In patients with stable CHD, more physical activity was associated with lower mortality. The largest benefits occurred between sedentary patient groups and between those with the highest mortality risk.
REFERENCE: *Stewart RAH et al. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. J Am Coll Cardiol. 2017 Oct 3;70(14):1689-1700.*

#8 Exercise reduces the risk of injurious falls in older adults

Clinical question: Are there specific interventions that are effective in reducing the risk of injurious falls in older adults?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, the Cochrane Register, Ageline, and reference lists of relevant trials and reviews for randomized controlled trials that examined fall-prevention interventions for adults 65 years or older. Study authors were also contacted for unpublished studies or additional data. Two investigators independently reviewed all potential studies for inclusion criteria and methodologic quality using standard risk-of-bias scoring tools. Conflicts were resolved by consensus agreement with a third reviewer. The primary outcome of interest was the number of injurious falls and fall-related hospitalizations. A total of 283 randomized trials and 20 companion reports (N = 159,910 participants) met inclusion criteria. The overall risk of bias among the studies was moderate, with an unclear risk of bias for allocation concealment, contamination, and selective outcome reporting. A funnel plot analysis found no evidence of publication bias. Four interventions were significantly associated with a reduced risk of injurious falls compared with usual care: exercise alone; combined exercise and vision assessment and treatment; combined exercise, vision assessment and treatment, and environmental assessment and modification; and combined clinic-level quality improvement strategies, multifactorial assessment and treatment, calcium supplementation and vitamin D supplementation. Combined exercise and vision assessment and treatment was the most effective intervention. In a subgroup analysis, the best intervention for reducing the risk of hip fracture was combined osteoporosis treatment, calcium supplementation, and vitamin D supplementation.
Bottom line: Exercise alone; exercise combined with vision assessment/treatment; exercise combined with vision assessment/treatment and environmental assessment/modification; and clinic-level quality improvement strategies combined with multifactorial assessment/treatment and calcium and vitamin D supplementation are all effective interventions for reducing the risk of injurious falls in older adults.
Tricco AC, Thomas SM, Veroniki AA, et al. Comparisons of interventions for preventing falls in older adults. A systematic review and meta-analysis. JAMA 2017; 318(17):1687-1699.

#9 Tai chi decreases the risk of falls in at-risk adults and elderly

Clinical question: Does tai chi decrease the risk of falls in at-risk adults and the elderly?
Study design: Meta-analysis (randomized controlled trials)
Setting: Outpatient (any)
Synopsis: These authors systematically searched several databases and the reference lists of retrieved articles to identify randomized trials of tai chi that reported fall rates. The authors tried to statistically assess for publication bias, but they do not describe a formal search for unpublished negative studies that could reduce the pooled benefit. Ultimately, they included 10 studies with 2645 participants. The study participants were generally older and had previous falls, though some studies included "pre-frail" elders or those at an increased risk of falls. Five studies reported that tai chi decreased the short-term risk of falls (relative risk [RR] = 0.57; 95% CI 0.46 - 0.70) and 6 studies reported a decrease in the long-term risk of falls (RR = 0.87; 0.77 - 0.99). Only one study, rated at high risk of bias, assessed falls that caused actual injury. Sadly, the authors don't report enough data to estimate the numbers needed to treat nor the rate of harms associated with tai chi. The authors report no significant heterogeneity in the data.
Bottom line: In this systematic review, tai chi was associated with a decreased risk of falls. However, only one low-quality study assessed injurious falls.
Lomas-Vega R, Obrero-Gaitan E, Molina-Ortega FJ, Del-Pino-Casado R. Tai chi for risk of falls. A meta-analysis. J Am Geriatr Soc 2017;65(9):2037-2043.

#10 Exercise = knee surgery for degenerative meniscal tear

Clinical question: Is arthroscopic surgery better than exercise therapy to treat symptoms associated with degenerative meniscal tears in middle-aged patients?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: The researchers (orthopedists practicing in Norway) enrolled 140 patients (between the ages of 35 and 60 years) who were referred for care for unilateral knee pain with medial degenerative meniscal tear confirmed by magnetic resonance imaging. Most (96%) had no or minimal radiographic changes associated with osteoarthritis. Pain had to be present for at least 2 months without a history of major knee trauma. The patients were randomized, using concealed allocation, to receive either exercise therapy 2 or 3 times weekly for 3 months or arthroscopic meniscectomy. There were no sham treatments; patients assigned to exercise did not get arthroscopy without meniscal repair and patients undergoing surgery did not have additional sham or actual exercise. Patients reported on pain, function, knee-related quality of life, and other symptoms using the knee injury and osteoarthritis outcome score. Using intention-to-treat analysis at 2 years, there was no difference between the 2 groups. Approximately 1 in 5 (19%) patients who received exercise therapy eventually underwent arthroscopic surgery without any additional benefit.
Bottom line: Despite a significant initial bump in benefit due to the placebo effect, arthroscopic meniscectomy in patients without a history of acute trauma and without a history of knee locking does not reduce pain and improve function after 2 years as compared with 3 months of exercise therapy. This study did not evaluate surgery with exercise versus exercise alone, but other studies have done so and found no additional benefit.
Kise NJ, Risberg MA, Stensrud S, Ranstam J, Engebretsen L, Roos EM. Exercise therapy versus arthroscopic partial meniscectomy for degenerative meniscal tear in middle aged patients: randomised controlled trial with two year follow-up. BMJ 2016 July 20;354:i3740.

#11 Early PT for acute low back pain is cost-effective, but gain in quality of life is likely too small to notice

Clinical Question: Is physical therapy cost-effective in the initial management of patients with acute low back pain?
Funding: Government
Setting: Outpatient (any)
Allocation: Unknown
Study Design: Cost-effectiveness analysis
Synopsis: A previous randomized trial compared early PT with delayed referral in primary care patients with acute low back pain. They found better short-term outcomes with early PT, and although the results were statistically significant, the effect sizes did not meet the prespecified criteria for a minimally clinically important difference. There were also no differences at 1 year. Of note, the PT consisted of only 4 sessions over 4 weeks, and the smoking rates were lower than in the general population. In this study, the authors used those results to determine if early PT was cost-effective when considering broader outcomes, such as lost productivity and impact on quality of life. They performed a basic cost-effectiveness analysis, although it is limited by only performing a sensitivity analysis for those patients with complete diary data. The model appears to be fairly simplistic, and was not performed using standard modeling software, such as TreeAge. They found that although early PT results in higher total costs in their adjusted analysis ($1442 vs $862 over 1 year), it was also associated with a small increase in QALYs (0.02) and quality of life scores. They calculated an incremental cost-effectiveness ratio of $29,000 per additional QALY and found a similar $32,058 per QALY using a bootstrapping analysis.
Bottom Line: At $30,000 per quality-adjusted life year (QALY) gained, early physical therapy (PT) for acute low back pain in primary care is cost-effective by the usual criteria of $50,000 to $100,000 per QALY. However, the magnitude of improvement in quality of life is small and is probably not clinically meaningful. PT is an option to consider if it is not too difficult to find nor too expensive for your patients. (LOE = 3b)
Reference: *Fritz JM, Kim M, Magel JS, Asche CV. Cost-effectiveness of primary care management with or without early physical therapy for acute low back pain: economic evaluation of a randomized clinical trial. Spine 2017;42(5):285-290.*

#12 Physical therapy doesn't add anything to standard treatment of ankle pain

Clinical question: In patients with mild to moderate ankle sprain, does physical therapy (physiotherapy) hasten or improve recovery?
Study design: Randomized controlled trial (nonblinded)
Setting: Emergency department
Synopsis: These authors studied the effect of longitudinal, supervised, stepwise physical therapy in addition to usual acute management of mild to moderate ankle sprain (grade 1 or 2) in 503 patients, 16 years or older, who presented to an emergency department in Canada. It's interesting that 84% of patients received an x-ray although approximately 30% of patients had mild (grade 1) sprain and any patients who required immobilization were excluded. One week after evaluation and basic management with RICES (rest, ice, compression, elevation, splinting), patients were randomized, using concealed allocation, to continue with usual care or to add stepwise physical therapy of up to seven 30-minute visits combined with home exercise. The main outcome was a score of "excellent" (at least 450) at 3 months on a 500-point patient questionnaire of symptoms, stiffness, pain, function, recreational activity, and quality of life. At 3 months approximately 40% of patients scored at least 450, with no difference between groups (42% vs 40%). After 6 months, the percentage of patients experiencing excellent recovery was slightly higher in the usual care group than in the intervention group, but the difference was not statistically significant between groups (65% vs 56%; P = .09). In addition to patient reports of symptoms and function, the researchers also conducted clinical and biomechanical evaluation, again not finding any difference between the groups. The study had the power of at least 80% to find an increase in excellent recovery from 60% to 75%, if one existed.
Bottom line: Physical therapy (up to 7 sessions) does not hasten resolution of symptoms or improve function in adults with ankle sprain: Approximately 60% of patients who receive usual care or physical therapy do not achieve "excellent" resolution. Send patients home with the usual RICES protocol: rest, ice, compression, elevation, and splinting.
Reference: *Brison RJ, Day AG, Pelland L, et al. Effect of early supervised physiotherapy on recovery from acute ankle sprain: randomised controlled trial. BMJ 2016;355:i5650.*

Exercise in Pregnancy

#13 Regular, moderately intense exercise during pregnancy is beneficial

Clinical question: Does a supervised exercise program during pregnancy reduce the risks of pregnancy complications?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: In this randomized controlled trial healthy pregnant women (N = 840) either participated in a supervised exercise program or received standard care. Women were included if they had an uncomplicated singleton pregnancy, no prior preterm birth, and no contraindications to exercise. The exercise intervention included three 50- to 55-minute sessions weekly from 9 to 11 weeks' gestation to 38 to 39 weeks' gestation (approximately 85 total sessions) conducted by a fitness professional at the hospital where the women received care. Each session included aerobic, resistance, and stretching exercises and consisted of a warm-up and cool-down of 10 minutes each and vigorous exercise for 25 to 30 minutes. Women in the control group were encouraged to exercise and would have been excluded if they reported regular exercise for more than 20 minutes daily (which no one did). Loss to follow-up was similar between groups. Preterm birth was similar between groups and those women were excluded from analysis. Compliance was high,

which may not be true of other populations. Women in the exercise group were less likely to develop hypertension (2.1% vs 5.7%; P = .009; number needed to treat [NNT] = 27, 95% CI 15-113) or to develop gestational diabetes (2.4% vs 5.5%; P = .03; NNT = 32, 16-290). Although mean weight gain was similar between groups, women in the exercise group were less likely to gain excessive weight (26% vs 34%; P = .03; NNT = 13, 7-80). Mean infant birth weight was not significantly different between groups, but the incidence of macrosomia (> 4000 g) was lower in the intervention group (1.8% vs 4.7%; P = .03; NNT = 35, 18-320). There were no differences in other secondary outcomes including gestational age at delivery, low birth weight, type of delivery, Apgar scores, or umbilical artery pH of the newborn at birth.
Bottom line: Healthy Spanish women who participated in a supervised exercise program from late first trimester until term were less likely to develop hypertension or gestational diabetes, to gain excess weight, or to give birth to a macrosomic infant. Similar interventions should be tested in other populations to determine whether these results are generalizable.
Reference: *Barakat R, Pelaez M, Cordero Y, et al. Exercise during pregnancy protects against hypertension and macrosomia: randomized clinical trial. Am J Obstet Gynecol 2016;214(5):649.e1-8.*

#14 Physical activity interventions in pregnancy decrease weight gain & risk of GDM

Clinical question: Do interventions to increase physical activity during pregnancy reduce the risks of excessive weight gain and gestational diabetes?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: For this meta-analysis of programs of physical activity during pregnancy the authors selected 13 unmasked randomized controlled trials (N = 2873 women). Studies were included if the participants were healthy women with singleton pregnancies whose physical activity level was fewer than 20 minutes 3 times weekly, the control group did not receive an exercise program, and the considered outcomes included GDM and maternal weight gain. The exercise interventions varied markedly in number, duration, and content. In all but 1 study the programs were supervised; the program was home-based in the remaining study. The methodology for the meta-analysis was thoroughly described and well-executed. Of the included studies 11 had adherence rates of greater than 85%. Drop-outs were also low overall, with 12 studies reporting rates of less than 20%. Only 2 studies were conducted in the United States. Only 4 studies provided intention-to-treat analysis. The calculated relative risk (RR) for GDM among the intervention groups was 0.69 (95% CI 0.52-0.91; P = .009). The weighted mean difference for weight gain was -1.14 kg (95% CI -1.5 to -0.78 kg; P < .001). In planned subgroup analyses the authors found that there was a lower risk of GDM when the program was implemented throughout the pregnancy than when it began in second trimester (RR 0.64, 95% CI 0.36-0.98; P = .038), without a corresponding effect on weight gain. There was also a lower risk of GDM with combined exercise programs that included aerobic exercise and resistance or strength training (RR 0.69, 95% CI 0.48-0.99; P = .043).
Bottom line: Structured programs of moderate physical exercise decreased the risk of gestational diabetes mellitus (GDM) and decreased maternal weight gain among otherwise healthy sedentary women. Programs that were continuous throughout the pregnancy had more benefit that those started in the second trimester. Programs that combined aerobic exercise and resistance or strength training were also more beneficial.
Sanabria-Martinez G, Garcia-Hermoso A, Poyatos-Leon R, Alvarez-Bueno C, Sanchez-Lopez M, Martinez-Vizcaino V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis. BJOG 2015;122(9):1167-1174.

#15 Cycling during pregnancy reduced the rate of GDM in overweight and obese women

Clinical question: Does a regular cycling exercise program in pregnancy reduce the risk of gestational diabetes mellitus in overweight and obese women?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: These investigators enrolled 300 overweight and obese women at 10 weeks' gestational age. The investigators used Chinese criteria to define overweight (BMI > 24 and < 28) and obesity (BMI at least 28). Eligible women were at least 18 years old, nonsmokers, with a singleton pregnancy. Women were excluded if they had cervical insufficiency or shortened cervix according to ultrasound (< 25 mm at < 24 weeks), were taking medication for any pre-existing chronic disease, or were currently being treated with metformin or corticosteroids. Allocation was concealed, but the study was otherwise unmasked. Women allocated to the exercise group attended supervised stationary cycling classes for 30 minutes at least 3 times per week, starting within 3 days of randomization and continuing until at least 36 weeks' gestation. All women, including the control patients, received general advice regarding the benefits of physical activity during pregnancy. Women in the exercise group were highly compliant, with 90% attending at least 80% of classes. Physical activity was estimated using the International Physical Activity Questionnaire at 25 weeks' gestation. The results in the cycling versus control groups were 1741 +/- 798 and 1327 +/- 1300 metabolic equivalent minutes per week, respectively. Among the 88% of participants who underwent screening for GDM, women in the cycling group had an incidence of 22% vs 41% among control patients (odds ratio 0.412; 95% CI 0.24 - 0.71; P < .001; number needed to treat = 5; 3 - 13). Gestational weight gain was significantly less among women in the cycling group (8.38 kg +/- 3.65 vs 10.47 +/- 3.33; P < .001). There were no differences in other maternal outcomes including hypertensive disorders, cesarean delivery, and gestational age at birth. There were no differences in incidence of macrosomia, large-for-gestational-age infants, or Apgar scores. Birthweight was lower in the cycling group by a mean of 100 g. There were also 3 small-for-gestational-age infants in the cycling group with none in the control group, but the sample size was too small for statistical analysis.
Bottom line: In this randomized controlled trial a supervised stationary cycling program started early in pregnancy reduced the incidence of gestational diabetes mellitus (GDM). Birthweight was also significantly lower in the cycling group by a mean of approximately 100 g, and the cycling group included 3 cases of infants who were small-for-gestational age. A larger study would be

required to determine whether the level of physical activity used in this intervention increases the risk of growth restriction. The study was conducted in a compliant Chinese population using Chinese body mass index (BMI) criteria, which is lower than the US criteria. *Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese women. Am J Obstet Gynecol 2017;216(4):340-351.*

Genetic Testing

#16 The role of genetic testing in athletic pre-participation cardiac screening

These authors from Belgium and the UK present a commentary on the ethics of genetic testing before sports participation. They introduce a hypothetical asymptomatic professional soccer player in his or her 20s (i.e., not a minor) who has an abnormal cardiac screen or a family history of sudden cardiac death. Genetic testing is problematic because genotype may not adequately predict disease phenotype (i.e., onset or severity), and some people will be genotype-positive but phenotype-negative. False-positive and false-negative rates of testing can, therefore, be high. Level of risk varies with the specific mutation and the type of sport involved. Family history (and physician liability) will lead to a low threshold for testing given that the first disease manifestation could be a fatal cardiac arrest. American and European guidelines differ on criteria for disqualification from sports participation, with the US requiring a threshold level of phenotypic expression and Europe requiring only a genetic mutation. Disqualification of an athlete from play is equivalent to loss of employment, and genetic testing is against the law for prospective employees in other venues, yet athletes may feel compelled to undergo further diagnostic testing. Diagnosis of a genetic condition has ramifications for psychological well-being, life and disability insurance, and livelihood. The ethics demand patient autonomy before cardiac screening and genetic testing, involvement of a genetics counselor, clear informed consent (including the right not to know the results), and confidentiality. Genetic testing should be performed by an independent team not associated with the cardiac screening so that the results are not used in sports eligibility decisions.
REFERENCE: *Magavern, E.F., et al, ETHICAL CONSIDERATIONS FOR GENETIC TESTING IN THE CONTEXT OF MANDATED CARDIAC SCREENING BEFORE ATHLETIC PARTICIPATION Genet Med 19(5):493, May 2017*

Bottom Lines

- Physical activity and sedentary time appear to be independently associated with all-cause mortality
- Deaths and cardiac arrests during the triathlon are ~ 1/100,000 participants
- Wearable technology has variable effects on outcomes
- Exercise is associated with better outcomes in patients with ischemic heart disease, fall risk in the elderly, degenerative meniscal tears and ankle sprain
- Exercise during pregnancy is associated with improved maternal an fetal outcomes
- Ethical considerations exist for athletic pre-participation genetic cardiac screening

GU Update John Hickner, MD

Objectives

1. Know the findings of recent studies regarding potential benefits and harms of screening for and treating prostate cancer
2. Review recent research regarding renal and bladder conditions pertinent to primary care practitioners.
3. Review recent evidence for the effectiveness of treatments for ureteral calculi and chronic kidney disease.

Prostate Cancer

The landscape of prostate cancer screening and treatment has changed greatly during the past 5 years. Because most prostate cancer is relatively indolent, active surveillance of low grade (Gleason 6) prostate cancer has expanded dramatically, with about half of US men choosing active surveillance. This has caused the USPSTF to reconsider the D recommendation for PSA screening and reclassify as a C recommendation for men 55 to 69.

"The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)–based screening for prostate cancer. The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older." (2018 recommendations.)

1. Active surveillance for localized prostate CA: no increased mortality, but higher rates of clinical progression (ProtecT)

Clinical question: What is the best approach to the management of localized prostate cancer?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (specialty)
Synopsis: Clinically localized prostate cancer is defined as stage T1c or T2 and is confined to the prostate gland. In this study, 82,429 British men aged 50 to 69 years had a prostate-specific antigen (PSA) test. Of those, 2664 had grade T1c or T2 cancer, and 1643 agreed to be randomized to 1 of 3 groups: radical prostatectomy, radiotherapy, or a program of AS. AS consisted of frequent PSA tests (every 3 months in the first year and every 6 to 12 months after that), with a rise of 50% or more triggering an evaluation for possible biopsy, and treatment, if indicated. Approximately 80% of men assigned to surgery or radiotherapy received the assigned treatment during the first year following randomization. In the AS group, there was a steady increase in the percentage of men who received radiotherapy, prostatectomy, or another treatment with curative intent, from 20% at year 2, to 40% at year 5, to slightly more than 50% at year 10. There was no difference between groups in mortality due to prostate cancer, in prostate cancer–specific survival at 5 or 10 years, or in all-cause mortality. However, there was a greater likelihood of developing metastatic disease in the AS group, with approximately 3 more metastatic cancers detected per 1000 person-years than in the surgery or radiotherapy groups (P = .004). Clinical progression (defined as progression to T3 or T4 disease, urinary or rectal complications, or the use of androgen deprivation therapy) was also more common in the AS group, with approximately 13 additional patients progressing per 1000 person-years. Stratification of patients by age, PSA result, Gleason score, or stage at diagnosis did not affect the results.
Bottom line: This landmark study compared active surveillance (AS) with radical prostatectomy or radiation therapy for patients with T1c or T2 prostate cancer. The benefits of AS include avoiding radical therapy in half the patients, with no effect on disease-specific survival or all-cause survival. The potential harms include a greater risk of metastatic disease (3 additional cases per 1000 person years, corresponding to 3 additional cases for 100 men followed up for 10 years) and a greater likelihood of clinical progression. An accompanying study (N Engl J Med 2016; 2016;375(15):1425-1437) discusses the effects on quality of life and complications of treatment.
Hamdy FC, Donovan JL, Lane JA, et al, for the ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375(15):1415-1424.

2. Prostatectomy for local prostate cancer does not significantly reduce mortality in up to 20 years of follow-up

Clinical question: For men with localized prostate cancer, does surgery improve long-term health outcomes?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)

Synopsis: This is a long-term follow-up of patients in the PIVOT trial, which compared radical prostatectomy with observation. Patients in each group saw a physician to assess progression of symptoms every 6 months and had bone scans every 5 years, although "active surveillance" was not practiced. All patients had localized (T1-G2NxM0) prostate cancer with a PSA level of less than 50 ng/mL, were younger than 75 years, and were expected to live at least 10 years. See our original review of the PIVOT trial for more details: http://www.essentialevidenceplus.com/content/poem/140901. In the current study, the authors report mortality data through 2014 (range: 12 years to 19.4 years) and provide additional details regarding disease progression and other health outcomes during the original study period (through 2010). Analyses were by intention to treat, and groups were balanced at the start of the study. There was a 5.5% absolute reduction in all-cause mortality and a 4% absolute reduction in prostate cancer–specific mortality at the end of follow-up. These differences were not statistically significant (P = .06 in both cases), but are potentially clinically significant. The absolute risk reductions were greater in patients younger than 65 years (12.2% vs 2.6%) and in those with an initial PSA level greater than 10 ng/mL, though these differences were not statistically significant due in part to small sample size for these subgroups. There was a statistically significant increase in all-cause mortality for patients in the intermediate-risk group based on the D'Amici risk score (in Essential Evidence at http://www.essentialevidenceplus.com/content/rules/304), but not in the low-risk or high-risk groups. The likelihood of disease progression was lower in the surgery group (33.0% vs 59.7%; P < .05; number needed to treat [NNT] = 4), although this was largely due to a greater likelihood of biochemical or local progression. Systemic progression (ie, metastasis) occurred less often in the radical surgery group (4.7% vs 8.7%; P < .05; NNT = 25), similar to the findings of the UK ProtecT trial (http://www.essentialevidenceplus.com/content/poem/181203). However, erectile dysfunction (14.6% vs 5.4%; P < .05; NNTH = 11) and incontinence (17.3% vs 4.4%, NNTH = 8) were also more common in the surgery group.
Bottom line: Radical prostatectomy has benefits and harms. There was a strong and consistent trend toward greater mortality in the PIVOT trial, which obtained a prostate-specific antigen (PSA) test every 6 months but left the subsequent follow-up to the individual physicians. But it is important to view this study in the context of the recent UK ProtecT trial, which used a more aggressive and structured active surveillance protocol. The UK study had higher rates of eventual treatment in the active surveillance arm than the PIVOT trial and found no difference in mortality. Both studies found similar but small increases in rates of progression to metastatic disease, and much higher rates of erectile dysfunction and incontinence in the surgery group. The reduction in mortality was greatest in younger patients and in those with a PSA level greater than 10 ng/mL (though the reduction was not statistically significant because of the small numbers in these subgroups).
Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of prostatectomy versus observation for early prostate cancer. N Engl J Med 2017;377(2):132-142.

Chronic Kidney Disease

Good news – the prevalence of chronic kidney disease has levelled off this past decade, perhaps due to better treatment of hypertension. USPSTF and ACP do not recommend routinely screening for chronic kidney disease, though we see patients with diminished kidney function every day in our offices as we care for patients with diabetes, hypertension and cardiovascular disease.

3. No Recent Increase in the Prevalence of Chronic Kidney Disease in the United States

Background: Trends in the prevalence of chronic kidney disease (CKD) are important for health care policy and planning.
Objective: To update trends in CKD prevalence.
Design: Repeated cross-sectional study.
Setting: NHANES (National Health and Nutrition Examination Survey) for 1988 to 1994 and every 2 years from 1999 to 2012.
Participants: Adults aged 20 years or older.
Measurements: Chronic kidney disease (stages 3 and 4) was defined as an estimated glomerular filtration rate (eGFR) of 15 to 59 mL/min/1.73 m2, estimated with the Chronic Kidney Disease Epidemiology Collaboration equation from calibrated serum creatinine measurements. An expanded definition of CKD also included persons with an eGFR of at least 60 mL/min/1.73 m2 and a 1-time urine albumin–creatinine ratio of at least 30 mg/g.
Results: The unadjusted prevalence of stage 3 and 4 CKD increased from the late 1990s to the early 2000s. Since 2003 to 2004, however, the overall prevalence has largely stabilized (for example, 6.9% prevalence in 2003 to 2004 and in 2011 to 2012). There was little difference in adjusted prevalence of stage 3 and 4 CKD overall in 2003 to 2004 versus 2011 to 2012 after age, sex, race/ethnicity, and diabetes mellitus status were controlled for (P = 0.26). Lack of increase in CKD prevalence since the early 2000s was observed in most subgroups and with an expanded definition of CKD that included persons with higher eGFRs and albuminuria.
Limitation: Serum creatinine and albuminuria were measured only once in each person.
Conclusion: In a reversal of prior trends, there has been no appreciable increase in the prevalence of stage 3 and 4 CKD in the U.S. population overall during the most recent decade.
Primary Funding Source: American Society of Nephrology Foundation for Kidney Research Student Scholar Grant Program, Centers for Disease Control and Prevention, and National Institutes of Health.
Murphy D, McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL, Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR, Hsu CY: Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. Trends in Prevalence of Chronic Kidney Disease in the United States. Ann Intern Med. 2016 Oct 4;165(7):473-481.

4. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation

DESCRIPTION: U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for chronic kidney disease (CKD).
METHODS: The USPSTF reviewed evidence on screening for CKD, including evidence on screening, accuracy of screening, early treatment, and harms of screening and early treatment.
POPULATION: This recommendation applies to asymptomatic adults without diagnosed CKD. Testing for and monitoring CKD for the purpose of chronic disease management (including testing and monitoring patients with diabetes or hypertension) are not covered by this recommendation.
RECOMMENDATION: The USPSTF concludes that the evidence is insufficient to assess the balance of benefits and harms of routine screening for CKD in asymptomatic adults (I statement).
Moyer VA; U.S. Preventive Services Task Force. Collaborators: Moyer VA, LeFevre ML, Siu AL, Baumann LC, Bibbins-Domingo K, Curry SJ, Ebell M, Flores G, Cantu AG, Grossman DC, Herzstein J, Melnikow J, Nicholson WK, Owens DK, Reyes C, Wilt TJ. Ann Intern Med. 2012;157:567-570.

5. Clinical Guidelines Committee of the American College of Physicians. Screening, monitoring, and treatment of stage 1 to stage 3 chronic kidney disease

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the screening, monitoring, and treatment of adults with stage 1 to 3 chronic kidney disease.
Methods: This guideline is based on a systematic evidence review evaluating the published literature on this topic from 1985 through November 2011 that was identified by using MEDLINE and the Cochrane Database of Systematic Reviews. Searches were limited to English-language publications. The clinical outcomes evaluated for this guideline included all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, chronic heart failure, composite vascular outcomes, composite renal outcomes, end-stage renal disease, quality of life, physical function, and activities of daily living. This guideline grades the evidence and recommendations by using ACP's clinical practice guidelines grading system.
Recommendation 1: ACP recommends against screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease. (Grade: weak recommendation, low quality evidence)
Recommendation 2: ACP recommends against testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II– receptor blocker. (Grade: weak recommendation, low-quality evidence)
Recommendation 3: ACP recommends that clinicians select pharmacologic therapy that includes either an angiotensin-converting enzyme inhibitor (moderate-quality evidence) or an angiotensin II– receptor blocker (high-quality evidence) in patients with hypertension and stage 1 to 3 chronic kidney disease. (Grade: strong recommendation)
Recommendation 4: ACP recommends that clinicians choose statin therapy to manage elevated low-density lipoprotein in patients with stage 1 to 3 chronic kidney disease. (Grade: strong recommendation, moderate-quality evidence)
Qaseem A, Hopkins RH Jr, Sweet DE, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Screening, monitoring, and treatment of stage 1 to 3 chronic kidney disease: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2013 Dec 17;159(12):835-47.

6. Chronic Kidney Disease: Detection and Evaluation

Chronic kidney disease affects 47 million people in the United States and is associated with significant health care costs, morbidity, and mortality. Because this disease can silently progress to advanced stages, early detection is critical for initiating timely interventions. Multiple guidelines recommend at least annual screening with serum creatinine, urine albumin/creatinine ratio, and urinalysis for patients with risk factors, particularly diabetes mellitus, hypertension, and a history of cardiovascular disease. The U.S. Preventive Services Task Force found insufficient evidence to assess the balance of benefits and harms of screening for chronic kidney disease in the general population, and the American College of Physicians recommends against screening asymptomatic adults without risk factors. Persistently elevated serum creatinine and albuminuria are diagnostic and prognostic hallmarks of chronic kidney disease. Lower levels of albuminuria are associated with adverse renal and cardiovascular outcomes. Serum cystatin C is a novel biomarker that is most useful when a false-positive decreased estimated glomerular filtration rate calculated from serum creatinine is suspected. New guidelines incorporate albuminuria into the classification framework for chronic kidney disease and elaborate on identification of the disease, the frequency of follow-up, and recommendations for nephrology referral. Nephrology consultation is indicated for patients with an estimated glomerular filtration rate less than 30 mL per minute per 1.73 m^2, persistent urine albumin/creatinine ratio greater than 300 mg per g or urine protein/creatinine ratio greater than 500 mg per g, or if there is evidence of a rapid loss of kidney function. A multidisciplinary approach between primary care physicians, nephrologists, and other subspecialists for implementing early interventions, providing education, and planning for advanced renal disease is key for effective management.
Gaitonde D, Cook D, Rivera I. Chronic Kidney Disease: Detection and Evaluation. Am Fam Physician. 2017 Dec 15;96(12):776-783.

The SPRINT trial showed better cardiovascular survival in older adults with high risk of cardiovascular disease, at the price of some decrease in renal function. Over the course of the 3 year trial, however, there was in increase in developing end stage renal disease. Empagliflozin (Jardiance), an SGLT-2 inhibitor, slowed decline of renal function of patients with type 2 diabetes in a randomized trial.

7. Intensive BP control in older patients can decrease renal function

Clinical question: Does intensive systolic blood pressure lowering in older patients increase the likelihood of renal dysfunction?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)

Synopsis: This report is a subgroup analysis of the SPRINT (Systolic blood Pressure Intervention Trial), which enrolled patients with high blood pressure and elevated cardiovascular risk. This analysis was limited to the 6662 participants, mean age 66 years, with a baseline estimated glomerular filtration rate (GFR) of at least 60 mL/min/1.73 m2, who represented approximately 70% of the total original cohort. The participants were randomly assigned, allocation concealment unknown, to be treated to reach an intensive (120 mm Hg or lower) or standard (140 mm Hg or lower) systolic blood pressure. The actual blood pressure difference between the 2 groups was an average 15 mm Hg. Significantly more people in lower blood pressure group experienced a significant decline in kidney function, defined as a 30% or greater decline in GFR to less than 60 mL/min/1.73 m2 (number needed to treat to harm = 38; 95% CI 29 - 53). But, as in the full SPRINT report, the risk of death or cardiovascular event over 3 years was lower with lower systolic blood pressure. None of the participants developed end-stage renal disease. Post-hoc analyses such as this one are risky to interpret, but in this case the results echo the analysis in the original report.
Bottom line: In this post-hoc analysis of the previously published SPRINT trial, lowering the systolic blood pressure of patients who are at increased risk of cardiovascular events (average age 66 years) will decrease their risk of cardiovascular disease but increase their likelihood of developing moderate renal dysfunction. It will not, at least over 3 years, increase their likelihood of developing end-stage renal disease.
Beddhu S, Rocco MV, Toto R, et al, for the SPRINT Research Group. Effects of intensive systolic blood pressure control on kidney and cardiovascular outcomes in persons without kidney disease. A secondary analysis of a randomized trial. Ann Intern Med 2017;167(6):375-383.

8. Empagliflozin slows progression of renal disease in very high-risk patients with T2DM

Clinical question: Does empagliflozin improve renal outcomes in patients with type 2 diabetes mellitus?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Empagliflozin works by reducing renal reabsorption of glucose, so patients urinate excess sugar. In this study, they recruited a very high-risk group of patients who had both T2DM and known cardiovascular disease. All patients had an estimated glomerular filtration rate (GFR) of at least 30 mL/min/1.73 m2. This study reports the renal outcomes; the primary outcome was a composite of progression to macroalbuminuria, a doubling of serum creatinine, having to start renal replacement therapy, or death due to renal disease. Patients had a mean age of 67 years if their GFR was 30 to 59, and 62 years if their GFR was 60 or higher. Most patients were men, nearly 80% had a history of coronary artery disease, approximately 25% had a history of stroke, and about 20% had a history of peripheral arterial disease. So, a very high-risk group indeed. The patients were randomized to empagliflozin 10 mg, empagliflozin 25 mg, or placebo. The analysis was by modified intention to treat, including all 7020 patients who received at least one dose of the study medication. A previous POEM (N Engl J Med 2015;373(22):2117-2128) found a significant reduction in all-cause mortality with treatment (NNT = 38 over 3.3 years). Progression to macroalbuminuria (11.2% vs 16.2%, NNT = 20), doubling of serum creatinine (1.5% vs 2.6%, NNT = 90), and, most important, need for renal replacement (0.3% vs 0.6%, NNT = 333) were all less likely with empagliflozin. Interestingly, there were 3 deaths due to renal disease in the treatment group, but none in the control group (P = NS). Genital infections and urinary tract infections were more common in the treatment group. There was no difference between groups by dose. This was an industry-sponsored trial and the sponsor participated in all aspects of the study.
Bottom line: Empagliflozin improves disease-oriented renal outcomes in patients with type 2 diabetes mellitus (T2DM), and provides a small reduction in the likelihood of requiring renal replacement therapy (number needed to treat [NNT] = 333 over 3.8 years). The cost is more than $300 per month, or nearly $5 million per patient who will avoid dialysis.
Wanner C, Inzucchi SE, lachin JM, et al, for the EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375(4):323-324.

Ureteral Stones

Do alpha-blockers increase the likelihood of passage of ureteral stones? The past few years have seen the pendulum swing back and forth – yes – no – yes. The evidence now appears solid that they do, for stones 5 mm to 10 mm. I think this illustrates how it often takes more than one study to discover the truth.

9. Tamsulosin = placebo for rate of 1-week stone passage in patients with urolithiasis

Clinical question: Is tamsulosin effective in facilitating stone passage in patients with kidney stones?
Study design: Randomized controlled trial (double-blinded)
Setting: Emergency department
Synopsis: Although tamsulosin is commonly used to facilitate the expulsion of kidney stones, the authors point out that the data is limited to a few flawed studies and only one randomized placebo-controlled trial. In this placebo-controlled randomized trial, the researchers randomly assigned 127 patients presenting to the emergency department with kidney stones to receive 0.4 mg tamsulosin or placebo and then followed them up for the next 7 days to determine stone passage, pain, analgesic use, and so forth. Of the enrolled patients, the authors excluded the 15 who were lost to follow up and the 12 who underwent surgery; exclusions which introduce bias in

favor of tamsulosin. At the end of 7 days, the rate of stone passage was statistically similar between patients taking tamsulosin and placebo (62% vs 54%), as was the degree of pain and the use of analgesics. This is considered a "negative" study. If the difference in the absolute event rate was statistically significant, one would only need to treat 13 patients to facilitate stone passage, which suggests the study was underpowered. Since the biases in this study favor tamsulosin and the study is underpowered, clear conclusions are difficult, but it is likely that tamsulosin is not effective in facilitating stone passage. Conclusions would have been much easier to make if the authors had done the study properly.
Bottom line: In this small, flawed study, tamsulosin (Flomax) was no more effective than placebo in facilitating the passage of kidney stones. Given the paucity of high-quality studies, can somebody please conduct a proper trial on this topic?
Berger DA, Ross MA, Hollander JB, et al. Tamsulosin does not increase 1-week passage rate of ureteral stones in ED patients. Am J Emerg Med 2015;33(12):1721-1724.

10. Tamsulosin effective as expulsion therapy for 5-mm to 10-mm distal ureteric stones

Clinical question: Is tamsulosin effective in the management of distal ureteric stones?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: These authors recruited adult patients who presented to the emergency department with symptoms and imaging consistent with distal ureteric stones. Patients with fever, hypotension, stones larger than 10 mm, or kidney disease were excluded. Using concealed allocation, the investigators randomized the patients to receive either tamsulosin 0.4 mg daily or matching placebo for 28 days or until stone passage. The 2 groups had similar baseline characteristics and analysis was by intention to treat. The primary outcome was stone expulsion as confirmed by computed tomography (CT) and time to stone expulsion was defined by self-reported passage of stone or 48-hour pain-free period. Compliance to the study medications was poor in both groups, and almost one-fifth of the patients did not have follow-up imaging. Of the approximately 80% of patients in each group who underwent follow-up CT, there was no difference in the percentage of patients with passed stones (87% in the tamsulosin group vs 82% in the placebo group; P = .22). In the subset of patients with larger stones (5 mm -10 mm), the tamsulosin group had a significantly higher rate of stone passage than the placebo group (83% vs 61%; P = .03). There were no significant differences detected in time to stone passage, pain, analgesia requirements, need for urological intervention, or adverse events.
Bottom line: Tamsulosin promotes stone passage of ureteric stones that are 5 mm to 10 mm. You would need to treat 5 patients with tamsulosin to cause the expulsion of one such stone. Stones smaller than 5 mm have a high rate of spontaneous passage without any intervention.
Furyk JS, Chu K, Banks C et al. Distal ureteric stones and tamsulosin: a double-blind, placebo-controlled, randomized, multicenter trial. Ann Emerg Med 2016;67(1):86-95.

11. Tamsulosin beneficial for passage of 5-mm to 10-mm distal ureteral stones

Clinical question: Is tamsulosin effective in promoting stone passage in patients with distal ureteral stones?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: The benefit of tamsulosin for the passage of ureteral stones 10 mm or smaller is uncertain given the conflicting results in recent randomized controlled trials. In this study, investigators searched MEDLINE, EMBASE, and CENTRAL databases, reviewed bibliographies of identified studies, and consulted with experts to find randomized double-blind placebo-controlled trials that evaluated the effectiveness of tamsulosin on the passage of ureteral stones that were 10 mm or smaller. Two reviewers independently selected studies, abstracted data, and performed a quality assessment. Eight studies with 1384 participants were included in the meta-analysis and all were considered at low risk for bias. Overall, 7 of the 8 studies enrolled only patients with distal ureteral stones. Tamsulosin 0.4 mg per day was used in all 8 studies, most commonly for 28 days. The outcome of interest was stone passage, defined in 7 studies as the absence of the stone on imaging and in 1 study as the absence of urologic intervention. Tamsulosin led to increased stone passage (85% vs 66%; risk difference 17%; 95% CI 6% - 27%), but there was significant heterogeneity in these results likely due to differences in outcomes based on stone size. Pre-planned subgroup analyses showed that tamsulosin was more effective than placebo for 5-mm to 10-mm distal stones (79% vs 57%; risk difference 22%; 12% - 33%; number needed to treat = 5) but not for those smaller than 5 mm. Since smaller stones are likely to pass spontaneously, treatment would not necessarily add any benefit. Increases in side effects, specifically dizziness and orthostatic hypotension, were not seen in the tamsulosin cohort, although there was much heterogeneity in the incidence of dizziness among the 8 trials. Finally, although there was evidence of publication bias, the authors did a thorough job of searching for possible unpublished reports and did not find any of high quality.
Bottom line: Tamsulosin promotes stone passage of distal ureteral stones that are 5 mm to 10 mm in size. You would need to treat 5 such patients in order to get one stone passage. Smaller stones tend to pass on their own at a rate of 86% in this study.
Wang RC, Smith-Bindman R, Whitaker E, et al. Effect of tamsulosin on stone passage for ureteral stones: a systematic review and meta-analysis. Ann Emerg Med 2016 Sep 7. pii: S0196-0644(16)30364-X. doi: 0.1016/j.annemergmed.2016.06.044. [Epub ahead of print].

12. Meta-analysis: alpha blockers effective for kidney stones

Clinical question: In patients with kidney stones (ureteric calculi), is treatment with an alpha blocker effective in improving passage rate and decreasing pain?
Study design: Randomized controlled trial (single-blinded)
Setting: Population-based

Synopsis: To conduct this study, the authors searched 5 databases (including Cochrane CENTRAL), a previous systematic review, reference lists of other reviews, and clinical trial registries. Two researchers independently selected randomized controlled trials that compared alpha blockers with placebo or no treatment in patients with ureteric stones. Two researchers independently extracted the data from 55 studies enrolling a total of 5990 patients. Stone passage, which occurs in approximately half of patients without intervention, is 50% greater with treatment (number needed to treat [NNT] = 3.74) and will occur an average 9.5 days after presentation as compared with 13.3 days without treatment. Episodes of pain will also be decreased. The need for surgery will decrease by approximately half (NNT = 6.17) and hospital admissions will decrease approximately 60% (NNT = 10.6) Patients with larger stones (at least 5 mm) are more likely to benefit. There was some evidence of publication bias; for some outcomes, results were calculated only using data from the larger studies. There was significant heterogeneity among the studies regarding stone passage rate.
Bottom line: Although a recent large study found no benefit to alpha blocker treatment (Lancet 2015;386:341-49), this meta-analysis of 55 studies found a benefit to using alpha blockers to increase the likelihood of stone passage, decrease surgical intervention, and decrease episodes of pain. These findings support European and US guidelines that recommend their use. Patients with larger (at least 5 mm) stones are more likely to benefit.
Hollingsworth JM, Canales BK, Rogers MA, et al. Alpha blockers for treatment of ureteric stones: systematic review and meta-analysis. BMJ 2016;355:i6112.

13. Water, medical treatments recommended to prevent kidney stones

Clinical question: What approaches should be taken for patients who have experienced nephrolithiasis?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This set of guidelines from the American College of Physicians is based on an evidence report sponsored by the Agency for Healthcare Research and Quality. Nephrolithiasis is just another in a long list of relatively common problems for which we have little evidence to support our common treatments. Based on low quality evidence, the group makes a weak recommendation to increase fluid intake to produce at least 2 L/day of urine, based mainly on its low risk and possible benefit. Other dietary interventions did not have enough support to make the recommendation list. Regarding drug therapy, monotherapy with thiazide diuretics, which block calcium excretion, will halve calcium stone recurrence (moderate-quality evidence). Similarly, potassium, potassium-magnesium, or potassium-sodium citrate will decrease calcium stone recurrence (moderate-quality evidence). Allopurinol has moderate-quality evidence that it reduces calcium oxalate stones. Combinations of these drug treatments do not seem to increase effectiveness. The guideline development group, including the chairman, was largely free of conflicts of interest. The committee included a methodologist but did not include a patient representative.
Bottom line: The American College of Physicians recommends enough fluid to result in 2 L of urine per day to prevent kidney stones in patients with a history of them. The group also recommends treatment with a thiazide diuretic or citrate in patients with recurrent calcium stones, and allopurinol in patients with calcium oxalate stones. These are all weak recommendations based on low-quality or moderate-quality evidence that benefits outweigh risks. The authors did not find convincing evidence that would support high-fiber or low-animal-protein diets, the prescription of mineral water, or the prohibition of cola-flavored soft drinks.
Qaseem A, Dallas P, Forciea MA, Starkey M, Denberg TD, for the Clinical Guidelines Committee of the American College of Physicians. Dietary and pharmacologic management to prevent recurrent nephrolithiasis in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2014;161(9):659-667. doi:10.7326/M13-2908.

Stress Incontinence and male pelvic pain syndrome

Electroacupuncture appears to be somewhat effective for stress incontinence in women and pelvic pain syndrome in men.

14. Electroacupuncture beneficial for women with stress urinary incontinence

Clinical question: Does electroacupuncture reduce urinary leakage and incontinence episodes in women with stress urinary incontinence?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: These investigators identified women, aged 40 years to 75 years, with involuntary loss of urine on physical exertion, sneezing, or coughing (stress UI) and with an incontinence pad weight gain greater than 1 g in the 1-hour pad test. Exclusion criteria included urge UI or mixed UI. The women, from multiple centers in China, randomly received (concealed allocation assignment) either active or sham electroacupuncture consisting of 18 sessions over 6 weeks. Both groups received acupuncture at bilateral locations in the third sacral foramen and lateral to the coccyx. Sham electroacupuncture consisted of the use of a placebo needle with no actual skin penetration and an electroacupuncture device with a broken inner wire and no actual current output. Individuals masked to treatment group assignment assessed outcomes. Complete follow-up occurred for 95.6% of participants at 30 weeks. The mean baseline urine leakage for both groups was 18 g. Using intention-to-treat analysis, reduction in the amount of urine leakage measured by the 1-hour pad test was significantly greater in the active electroacupuncture group than in the sham electroacupuncture group (mean difference 7.4 g; 95% CI 4.8 - 10.0). Similarly, a 50% or more reduction in the mean number of 72-hour incontinence episodes occurred significantly more often in the active group versus sham group (between-group difference at 30 weeks 25.6%; number needed to treat = 3.9; 3.0 - 6.0). The percentage of patients who correctly guessed their treatment group assignment was similar in both groups.

Bottom line: Active electroacupuncture (compared with sham electroacupuncture) significantly reduced the volume of urine leakage and the mean number of 72-hour incontinence episodes in women with stress urinary incontinence (UI).
Liu Z, Liu Y, Xu H, et al. Effect of electroacupuncture on urinary leakage among women with stress urinary incontinence. A randomized clinical trial. JAMA 2017;317(24):2493-2501.

15. Acupuncture effective for chronic prostatitis/chronic pelvic pain syndrome in men

Clinical question: Is acupuncture an effective treatment for adult men with chronic prostatitis/chronic pelvic pain syndrome?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: These investigators identified men aged 18 years to 50 years who'd met the standard diagnostic criteria for chronic prostatitis/chronic pelvic pain for a minimum of 3 of the last 6 months. A total of 68 patients randomly received assignment (concealed allocation) to treatments with acupuncture or sham acupuncture. Participants attended 3 sessions per week for 8 consecutive weeks, with each session lasting approximately 30 minutes. Active treatment consisted of acupuncture needle insertion and twirling stimulation at pelvic and sacral acupoints. Sham acupuncture consisted of stimulation at the same acupoints with a blunt-tip needle that did not penetrate the skin. Individuals masked to treatment group assignment assessed outcomes using validated pain and quality-of-life measurement tools. Complete follow up occurred for 94.1% of participants at 32 weeks. Using intention-to-treat analysis, the decrease from baseline in the total symptom score at 32 weeks was 7.4 points lower (on a scale from 0 to 43; 95% CI 9.8 to 5.1) in the acupuncture group than in the sham acupuncture group, respectively, with a predetermined clinically significant difference of a 4-point decrease. The number of patients with a 50% decrease from baseline in the total symptom score was also significantly higher at 32 weeks in the active acupuncture compared to sham acupuncture group (56.3% vs 0.0%, respectively; number needed to treat = 1.9; 1.5 - 3.0). No significant difference was found between the groups in the number of patients who guessed whether they received traditional or sham acupuncture.
Bottom line: This study found that an 8-week treatment program with traditional acupuncture was superior to sham acupuncture in reducing pain and improving quality of life in men with chronic prostatitis/chronic pelvic pain syndrome.
Qin Z, Zang Z, Zhou K, et al. Acupuncture for chronic prostatitis/chronic pelvic pain syndrome: A randomized, sham acupuncture controlled trial. J Urol 2018;200(4):815-822.

Urinary Tract Infections

16. Analgesic-only treatment for UTI is an option for some

Clinical question: Does every woman with a urinary tract infection need antibiotic treatment, or can they choose to start with analgesia only?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: The German investigators enrolled 484 adult nonpregnant women who presented with typical symptoms of UTI without risk factors or complications. Although diagnostic testing was conducted, all women who presented with symptoms were enrolled (76% were culture-positive). Almost 60% of the women reported having symptoms for 2 days or fewer. The women were randomized, using concealed allocation, to receive either treatment with a single dose of the antibiotic fosfomycin (Monuril, Monurol, Monural) 3 g or ibuprofen 400 mg 3 times per day for 3 days (both with matched placebo). Over the subsequent 28 days, 34% of analgesic-treated women also received antibiotic treatment for UTI. By 4 days after presentation, 56% of antibiotic-treated women were symptom free as compared with 39% of analgesic-treated women (number needed to treat = 5.8; 95% CI 3.8 - 11.8). Total symptom duration was about 1 day fewer, on average, with antibiotic treatment (4.6 vs 5.6 days; P <.001). Symptom severity and limitation of activity was significantly lower in antibiotic-treated women. However, the number of women who experienced worsening symptoms, febrile UTI, or recurrence over the next 4 weeks was similar between the 2 groups. Antibiotic use, the primary outcome of this study, was less in the analgesic-treated group. Pyelonephritis was unusual but occurred more often in the analgesic-treated group (2% vs 0.4%) but a larger study will be needed to determine whether the difference is statistically significant.
Bottom line: Analgesic-only treatment may be an option for women with presumed urinary tract infection (UTI) who present early with mild to moderate symptoms. Their symptoms will be greater and will last a day longer, and approximately 1 in 3 will eventually get antibiotic treatment. However, the long-term results will be similar. This study used ibuprofen as the analgesic since the local analgesic phenazopyridine (Pyridium, Azo-Standard) is not commonly used in Germany where the study was conducted.
Gágyor I, Bleidorn J, Kochen MM, et al. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ 2015;351:h6544.

17. Increased water intake decreases UTI recurrence in women

Clinical Question: Does increased water intake decrease urinary tract infection recurrence in women?
Study Design: Randomized controlled trial (nonblinded) **Funding:** Industry
Setting: Outpatient (any) **Allocation:** Concealed
Synopsis: These researchers enrolled 140 premenopausal women with 3 or more documented episodes of lower UTI but not pyelonephritis in the previous year. In this unblinded study (What is a suitable placebo for water?), the women were randomized, using concealed allocation, to continue their normal levels of water intake or to drink an additional 1.5 liters (3 bottles) of Evian-branded water daily for 12 months, which participants, on average, were able to maintain. Women in the extra water group had approximately half as

many infections as the usual intake group, an average 1.7 documented UTIs over the year as compared with an average 3.2 infections in the usual intake group (P < .001). All that extra water resulted in an additional 2 more trips to the bathroom every day, on average, than the usual intake group.
Bottom Line: Drinking an additional 1.5 liters per day of water halved the recurrence of urinary tract infection (UTI) in women with a history of at least 3 episodes per year. (LOE = 1b-)
Hooton TM, Vecchio M, Iroz A, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections. JAMA Intern Med 2018;178(11):1509-1515

18. Seven days vs. 14 days of antibiotic treatment for febrile UTI

BACKGROUND: In adults with febrile urinary tract infection (fUTI), data on optimal treatment duration in patients other than non-pregnant women without comorbidities are lacking.
METHODS: A randomized placebo-controlled, double-blind, non-inferiority trial among 35 primary care centers and 7 emergency departments of regional hospitals in the Netherlands. Women and men aged ≥ 18 years with a diagnosis of fUTI were randomly assigned to receive antibiotic treatment for 7 or 14 days (the second week being ciprofloxacin 500 mg or placebo orally twice daily). Patients indicated to receive antimicrobial treatment for at least 14 days were excluded from randomization. The primary endpoint was the clinical cure rate through the10- to 18-day post-treatment visit with preset subgroup analysis including sex. Secondary endpoints were bacteriologic cure rate at 10-18 days post-treatment and clinical cure at 70-84 days post-treatment.
RESULTS: Of 357 patients included, 200 were eligible for randomization; 97 patients were randomly assigned to 7 days and 103 patients to 14 days of treatment. Overall, short-term clinical cure occurred in 85 (90%) patients treated for 7 days and in 94 (95%) of those treated for 14 days (difference -4.5%; 90% CI, -10.7 to 1.7; P non-inferiority = 0.072, non-inferiority not confirmed). In women, clinical cure was 94% and 93% in those treated for 7 and 14 days, respectively (difference 0.9; 90% CI, -6.9 to 8.7, P non-inferiority = 0.011, non-inferiority confirmed) and, in men, this was 86% versus 98% (difference -11.2; 90% CI -20.6 to -1.8, P superiority = 0.025, inferiority confirmed). The bacteriologic cure rate was 93% versus 97% (difference -4.3%; 90% CI, -9.7 to 1.2, P non-inferiority = 0.041) and the long-term clinical cure rate was 92% versus 91% (difference 1.6%; 90% CI, -5.3 to 0.4; P non-inferiority = 0.005) for 7 days versus 14 days of treatment, respectively. In the subgroups of men and women, long-term clinical cure rates met the criteria for non-inferiority, indicating there was no difference in the need for antibiotic retreatment for UTI during 70-84 days follow-up post-treatment.
CONCLUSIONS: Women with fUTI can be treated successfully with antibiotics for 7 days. In men, 7 days of antibiotic treatment for fUTI is inferior to 14 days during short-term follow-up but it is non-inferior when looking at longer follow-up.
van Nieuwkoop C, van der Starre WE, Stalenhoef JE, van Aartrijk AM, et. al. Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind, placebo-controlled non-inferiority trial in men and women. BMC Med. 2017 Apr 3;15(1):70.

Bottom lines

1. PSA screening with shared decision making is an acceptable approach to prostate cancer screening.
2. Screening the general population for chronic kidney disease is not recommended.
3. Intensive blood pressure control in older adults can lead to renal function decline over 3 years. The significance of this decline is uncertain.
4. Empagliflozin slows renal function decline in patients with type 2 diabetes.
5. Alpha blockers increase the likelihood of passage of stones 5mm to 10mm only.
6. Lots of fluids, a thiazide diuretic or citrate in patients with recurrent calcium stones, and allopurinol in patients with calcium oxalate stones helps prevent recurrent kidney stones.
7. Electroacupuncture is somewhat effective for stress incontinence in women.
8. Increasing water intake by 1.5 liters a day halves the incidence of recurrent UTIs in women.
9. Bladder infections often resolve with no antibiotic treatment.
10. 7 days antibiotic treatment is sufficient for women with febrile UTI, but 14 days is better for men.

Lipids — Gary Ferenchick MD

Objectives

Understand:

1. The USPSTF recommendations on statin use in adults aged 40 -75
2. The USPSTF recommendations on screening for lipid disorders in children (aged < 20)
3. That major guidelines on statin therapy differ
4. That nonfasting lipid profiles are minimally different than fasting profiles
5. Some strategies for managing statin associated muscle symptoms (SAMS)
6. Outcome data and cost concerning PCSK9 antibodies
7. The ACC AHA guidance on non-stain therapies for ASCVD

USPSTF Recommendations on statin use (verbatim)

- The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (ie, symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. (Grade B | Offer or provide this service.)
- Although statin use may be beneficial for the primary prevention of CVD events in some adults with a 10-year CVD event risk of less than 10%, the likelihood of benefit is smaller, because of a lower probability of disease and uncertainty in individual risk prediction. Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 7.5% to 10%. (Grade C | Offer or provide this service for selected patients depending on individual circumstances.)
- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating statin use for the primary prevention of CVD events and mortality in adults 76 years and older without a history of heart attack or stroke. (Grade I | If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.)

In the clinical considerations, section of the document the USPSTF concluded that for primary prevention in those aged 40-75 with at least one risk factor, use of low- or moderate-dose statins was associated with *reduction* of:

- All-cause mortality | 14%
- CV mortality | 31%
- Ischemic CVA | 29%
- MI | 36%
- Composite CV outcomes | 30%

Statins used in primary prevention trials

	Low Dose (mg)	Moderate Dose (mg)
Atorvastatin		10-20
Fluvastatin	20 - 40	40 twice daily
Fluvastatin extended release		80
Lovastatin	20	40
Pitavastatin	1	2 - 4
Pravastatin	10 - 20	40 - 80
Rosuvastatin		5 - 10
Simvastatin	10	20 - 40
USPSTF | Accessed January 27 2018		

1. USPSTF recommends statin use for adult s aged 40 – 75 for primary prevention of CVD

Clinical question: What are the benefits and harms of statin treatment for dyslipidemia in adults 21 years and older?
Study design: Practice guideline
Setting: Population-based
Synopsis: The USPSTF found adequate evidence of a benefit of low- to moderate-dose statins for reducing the probability of CVD events and mortality in adults aged 40 to 75 years with at least 1 CVD risk factor and a calculated 10-year CVD event risk of 10% or greater. In addition, the harms of low- to moderate-dose statins in adults aged 40 to 75 years are small. Although myalgia is a commonly reported adverse effect of statin use, controlled trial data do not support any increased risk of myalgia with the use of statins compared with placebo. The USPSTF recognizes that the best currently available risk-estimation tool in the United States uses the Pooled Cohort Equations calculator from the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Since this tool has been shown to overestimate actual risk, clinicians should use the results to discuss with individual patients whether they want to pursue lifelong statin therapy. The current recommendations do not apply to adults with a low-density lipoprotein cholesterol level greater than 190 mg/dL (4.9 mmol/L). The USPSTF does not recommend for or against the use of C-reactive protein levels as a risk factor in screening for CVD. There is also insufficient evidence that screening for dyslipidemia before age 40 is beneficial in preventing CVD. The ACC/AHA recommends statin use for primary prevention in adults aged 40 to 75 years with an estimated 10-year CVD event risk from 7.5% to 10%.
Bottom line: The United States Preventive Services Task Force (USPSTF) now recommends that adults without a history of cardiovascular disease (CVD) use a low- to moderate-dose statin for the primary prevention of CVD events when ALL THREE of the following criteria are met: The patient (1) is 40 to 75 years old; (2) has at least one CVD risk factor (ie, dyslipidemia, diabetes, hypertension, or smoking); and (3) has a calculated 10-year risk of a CVD event of 10% or greater (B recommendation). The USPSTF further concludes that statin use may be beneficial for the primary prevention of CVD events in some adults aged 40 to 70 years with at least 1 CVD risk factor and a 10-year CVD event risk of 7.5% to 10%, although the likelihood of benefit is smaller (C recommendation). Finally, current evidence is insufficient to assess whether to initiate statin therapy for prevention of CVD events in adults 76 years or older (I statement).
Bibbins-Domingo K; US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults. US Preventive Services Task Force recommendation statement. JAMA 2016;316(19):1997-2007.

2. Lipid treatment for primary prevention not effective in older adults

Clinical question: In patients older than 65 years with elevated low-density lipoprotein levels but no cardiovascular disease, is cholesterol lowering effective in decreasing mortality or morbidity?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (any)
Synopsis: This report is an analysis of a trial that evaluated the primary prevention of cardiovascular disease using cholesterol lowering. It focused on patients who were at least 65 years old and had an elevated fasting low-density lipoprotein cholesterol (LDL-C) level (120 - 189 mg/dL [3.1 - 4.9 millimoles/L]). The Lipid-Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) study enrolled 2867 adults 65 years or older with hypertension but without baseline atherosclerotic cardiovascular disease. The patients were randomized, using concealed allocation, to receive usual care or pravastatin 40 mg daily. Most of the patients in the usual care group were not treated with a statin. Over the 6 years of follow-up, all-cause mortality was not different between the 2 treatment groups for patients 65 to 74 years of age (hazard ratio for pravastatin vs usual care = 1.08 (95% CI, 0.85-1.37; P = .55) and was almost statistically higher for patients at least 75 years of age (hazard ratio of pravastatin vs usual care = 1.34 (0.98-1.84; P = .07). Rates of coronary heart disease events were not different between the groups in either age group. Analysis was by intention to treat. Given that this is a post-hoc analysis, the researchers did not provide a power calculation and there might be a small difference in rates that was not see in this study.
Bottom line: If a patient makes it to 65 years old without developing cardiovascular disease, lowering his or her cholesterol level at this point is not effective, and might even be harmful if treatment is started at age 75. Given the lack of benefit also shown in other studies, it might be time to stop checking—and treating—high cholesterol in these age groups.
***Reference**: Han BH, Sutin D, Williamson JD, et al, for the ALLHAT Collaborative Research Group. Effect of statin treatment vs usual*

care on primary cardiovascular prevention among older adults. The ALLHAT-LLT randomized clinical trial. JAMA Intern Med 2017; doi:10.1001/jamainternmed.2017.1442.

3. USPSTF (I) recommendation for lipid screening in children

METHODS: The authors, writing for the USPSTF, present a clinical practice guideline that addresses screening for lipid disorders in asymptomatic children and adolescents aged 20 years or younger, representing an update to its 2007 guideline. The panel assessed the balance of benefits and harms based on two systematic reviews of the evidence in populations with heterozygous familial hypercholesterolemia (an autosomal dominant disorder of mutations in the LDL receptor gene) or multifactorial dyslipidemia (primarily due to obesity).
RESULTS: US estimates show that 8% of children aged 8-17 have elevated total cholesterol levels (200 mg/dL or higher) and 7% aged 12-19 have elevated LDL cholesterol levels (130 mg/dL or higher). Lipid elevations in general reportedly increase the risk of atherosclerosis and cardiovascular disease (CVD) events. The USPSTF found inadequate evidence that pharmacotherapy or lifestyle changes substantially reduce lipid parameters, atherosclerosis markers or premature CVD in persons with either familial hypercholesterolemia or multifactorial dyslipidemia. Evidence was also inadequate to assess the harms of screening or long-term treatment, although overdiagnosis is possible in children with multifactorial dyslipidemia. Differences in the diagnostic yield of universal versus selective screening could not be determined. It is also unclear whether changes in lipid levels or atherosclerotic parameters directly correlate with improvements in adult CVD outcomes.
CONCLUSIONS: Evidence is insufficient to assess the benefit-risk balance of screening for lipid disorders in persons aged 20 years or younger. It is suggested that obese children older than six years should be referred for behavioral interventions. 33 references (chair@uspstf.net – no reprints)
REFERENCE*: The USPSTF. SCREENING FOR LIPID DISORDERS IN CHILDREN AND ADOLESCENTS: US PREVENTIVE SERVICES TASK FORCE RECOMMENDATION STATEMENT. JAMA 316(6):625, August 9, 2016*

Major Guidelines on Statin Therapy Differ

In the past 5 years, the following organizations have published major guidelines on statins for primary prevention of ASCVD:

- American College of Cardiology/American Heart Association (ACC/AHA | 2013)
- United Kingdom's National Institute for Health and Care Excellence (NICE | 2014)
- Canadian Cardiovascular Society (CCS | 2016)
- U.S. Preventive Services Task Force (USPSTF | 2016)
- European Society of Cardiology/European Atherosclerosis Society (ESC/EAS | 2016)

The five guidelines have substantial differences (in spite of being founded on the same evidence) in the:

- recommended prediction model for ASCVD
- risk threshold
- low-density lipoprotein cholesterol (LDL-C) cut point for assignment of statin use

According to Mortensen (abstract #4)

"…statin therapy now constitutes the cornerstone of all major ASCVD prevention guidelines and has become the most commonly prescribed class of medication in the United States and Europe." Given this they did a "…head-to-head comparison of the 5 major guidelines in a contemporary cohort, in which 45,750 participants were selected from the general population, were aged 40 to 75 years, and were free of ASCVD and did not use statins at baseline between 2003 and 2009".

The following table shows the overall agreement between these guidelines in stating treatment (or not) for primary prevention in adults 40 – 75 years of age. Table from Ann Intern Med. 2018 Jan 16; 168(2):85-92)

Supplement Table 4. Overall agreement in statin recommendation (to treat or not to treat) between five major guidelines on statin use for primary prevention. The percentages were calculated as the number of individuals recommended for statin by both guidelines + the number of individuals not recommended for statin by both guidelines (number shown in the cells of the table) divided by the total number of individuals aged 40-75 years in Copenhagen General Population Study (n=45750).

All

Guidelines	*CCS*	*ACC/AHA*	*NICE*	*USPSTF*
CCS				
ACC/AHA	37343/45750 (82%)			
NICE	38089/45750 (83%)	40526/45750 (89%)		
USPSTF	37057/45750 (81%)	39802/45750 (87%)	40618/45750 (89%)	
ESC/EAS	31611/45750 (69%)	30008/45750 (66%)	33666/45750 (74%)	33162/45750 (72%)

4. Statin guidelines recommending more persons use statins prevent more events

Background: Five major organizations recently published guidelines for using statins to prevent atherosclerotic cardiovascular disease (ASCVD): in 2013, the American College of Cardiology/American Heart Association (ACC/AHA); in 2014, the United Kingdom's National Institute for Health and Care Excellence (NICE); and in 2016, the Canadian Cardiovascular Society (CCS), the U.S. Preventive Services Task Force (USPSTF), and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS).
Objective: To compare the utility of these guidelines for primary prevention of ASCVD.
Design: Observational study of actual ASCVD events during 10 years, followed by a modeling study to estimate the effectiveness of different guidelines.
Setting: The Copenhagen General Population Study.
Participants: 45 750 Danish persons aged 40 to 75 years who did not use statins and did not have ASCVD at baseline.
Measurements: The number of participants eligible to use statins according to each guideline and the estimated number of ASCVD events that statins could have prevented.
Results: The percentage of participants eligible for statins was 44% by the CCS guideline, 42% by ACC/AHA, 40% by NICE, 31% by USPSTF, and 15% by ESC/EAS. The estimated percentage of ASCVD events that could have been prevented by using statins for 10 years was 34% for CCS, 34% for ACC/AHA, 32% for NICE, 27% for USPSTF, and 13% for ESC/EAS.
Limitation: This study was limited to primary prevention in white Europeans.
Conclusion: Guidelines recommending that more persons use statins for primary prevention of ASCVD should prevent more events than guidelines recommending use by fewer persons.
Primary Funding Source: Copenhagen University Hospital.
Reference*: Mortensen MB, Nordestgaard BG.Comparison of Five Major Guidelines for Statin Use in Primary Prevention in a Contemporary General Population. Ann Intern Med. 2018 Jan 16;168(2):85-92.*

Non Fasting Lipids

Mora et al have concluded that studies show "... clinically insignificant differences between fasting and nonfasting levels for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. Prospective studies and meta-analyses have found that nonfasting lipids correlate with cardiovascular risk (ie, clinical events and mortality) at least as well as fasting measurements. (JAMA Intern Med. 2016 Jul 1;176(7):1005-6). Note however, the ACC still endorses fasting lipid assessments for initial assessment and follow up assessments.

5. Non-fasting blood samples should be routinely used for lipid assessment

AIMS: To critically evaluate the clinical implications of the use of non-fasting rather than fasting lipid profiles and to provide guidance for the laboratory reporting of abnormal non-fasting or fasting lipid profiles.

METHODS AND RESULTS: Extensive observational data, in which random non-fasting lipid profiles have been compared with those determined under fasting conditions, indicate that the maximal mean changes at 1-6 h after habitual meals are not clinically significant [+0.3 mmol/L (26 mg/dL) for triglycerides; -0.2 mmol/L (8 mg/dL) for total cholesterol; -0.2 mmol/L (8 mg/dL) for LDL cholesterol; +0.2 mmol/L (8 mg/dL) for calculated remnant cholesterol; -0.2 mmol/L (8 mg/dL) for calculated non-HDL cholesterol]; concentrations of HDL cholesterol,apolipoprotein A1, apolipoprotein B, and lipoprotein(a) are not affected by fasting/non-fasting status. In addition, non-fasting and fasting concentrations vary similarly over time and are comparable in the prediction of cardiovascular disease. To improve patient compliance with lipid testing, we therefore recommend the routine use of non-fasting lipid profiles, while fasting sampling may be considered when non-fasting triglycerides >5 mmol/L (440 mg/dL). For non-fasting samples, laboratory reports should flag abnormal concentrations as triglycerides ≥2 mmol/L (175 mg/dL), total cholesterol ≥5 mmol/L (190 mg/dL), LDL cholesterol ≥3 mmol/L (115 mg/dL), calculated remnant cholesterol ≥0.9 mmol/L (35 mg/dL), calculated non-HDL cholesterol ≥3.9 mmol/L (150 mg/dL), HDL cholesterol ≤1 mmol/L (40 mg/dL), apolipoprotein A1 ≤1.25 g/L (125 mg/dL), apolipoprotein B ≥1.0 g/L (100 mg/dL), and lipoprotein(a) ≥50 mg/dL (80th percentile); for fasting samples, abnormal concentrations correspond to triglycerides ≥1.7 mmol/L (150 mg/dL). Life-threatening concentrations require separate referral when triglycerides >10 mmol/L (880 mg/dL) for the risk of pancreatitis, LDL cholesterol >13 mmol/L (500 mg/dL) for homozygous familial hypercholesterolaemia, LDL cholesterol >5 mmol/L (190 mg/dL) for heterozygous familial hypercholesterolaemia, and lipoprotein(a) >150 mg/dL (99th percentile) for very high cardiovascular risk.
CONCLUSION: We recommend that non-fasting blood samples be routinely used for the assessment of plasma lipid profiles. Laboratory reports should flag abnormal values on the basis of desirable concentration cut-points. Non-fasting and fasting measurements should be complementary but not mutually exclusive.
REFERENCE: *Nordestgaard BG et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016 Jul 1;37(25):1944-58.*

The following is from the ACC AHA 2018 lipids guidelines (J Am Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X)

Adults > 20, order either **fasting or non-fasting lipid profile** (repeat fasting if initial TG's are > 400 mg/dL)

- "After normal food intake, LDL-C differs minimally with time."
- "Fasting and nonfasting TC and HDL-C levels appear to have fairly similar prognostic value and associations with CVD outcomes"

Statin Associated Muscle Symptoms (SAMS)

In abstract # 6 (below) SAMS is defined as the "inability to tolerate two or more statins, 1 at low dose, because of unexplained skeletal muscle related symptoms (for example pain aches weakness or cramping on) that began or increased during statin treatment and resolved with statin discontinuation"

The prevalence of SAMS is noted to be between 7% and 29% in registries of observational studies. SAMS includes a broad range of clinical presentations commonly with normal or minimally elevated CK levels. Statin associated myopathy with significant CK elevations occurs in ~ 1 per 10,000 people per year on standard doses.

In the Odyssey alternative trial 14% of patients failed to complete the run in period **on placebo** due to muscle related symptoms in the absence of statin exposure

No specific diagnostic markers for SAMS, he symptoms are generally subjective and no gold standard diagnostic test exists. According to Laufs …: Typical signs and symptoms include pain, tenderness, cramps and muscle weakness during physical activity or at night; commonly starting in the calves and thighs (seldom noted in the shoulders buttocks her arms); and increasing in intensity after 3-4 weeks of treatment"

Key elements of the recommendations concerning SAMS include:

- Shared decision making

- Withdrawal of statin therapy followed by one or more rechallenges (after 2-4 week washout) | restart at the lowest dose, and only increasing the dose every 4-12 weeks OR use of intermittent (non-daily) statin (such as rosuvastatin which is long-acting)
- Use of an alternative statin (not all statins are the same) | simvastatin atorvastatin and lovastatin are lipophilic and might be at the highest risk for SAMS; alternatives including pravastatin and fluvastatin are hydrophilic and have less muscle penetration and may be associated with a lower risk of SAMS
- Check CPK at baseline, do not start lipid-lowering therapy if the baseline CK is elevated (greater than 4 times upper limit of normal) in the absence of recent physical activity
- Repeat CK only if the patient develops symptoms
- Finally with regards to vitamin D and coenzyme Q 10; the authors note that there is no routine role for the use of vitamin D or CoQ10 in patients with SAMS | however they do note "vitamin D supplementation appears to benefit a majority of statin intolerant vitamin D deficient patients" and "88-95% of statin intolerant patient's were able to take statin rechallenge without any muscle symptoms once serum vitamin D was normalized"

6. Recommendations for SAMS

BACKGROUND AND AIMS: Statin-associated muscle symptoms (SAMS) frequently cause statin non-adherence, switching and discontinuation, contributing to adverse cardiovascular (CV) outcomes. Therefore, the management of SAMS is key in the effective treatment of patients with cardiovascular disease (CVD), through achievement of maximum-tolerated statin dosing and other practical aspects. The aim of this article is to provide practical, focused advice for healthcare professionals on the management of patients with SAMS.
METHODS: An expert working group combined current evidence, published guidelines and experiences surrounding a number of topics concerning SAMS to provide recommendations on how to best assess and manage this condition and reach the highest tolerated dose of statin for each individual patient.
RESULTS: The group collaborated to provide guidance on definitions in the SAMS field, psychological issues, re-challenging and switching treatments, as well as interpretation of current guidelines and optimal treatment of SAMS in different patient populations. An algorithm was developed to guide the management of patients with SAMS. In addition, the expert working group considered some of the more complex scenarios in a series of frequently asked questions and suggested answers.
CONCLUSIONS: The expert working group gave recommendations for healthcare professionals on the management of SAMS but highlighted the importance of tailoring the treatment approach to each individual patient. Evidence supporting the role of nutraceuticals and complementary therapies, such as vitamin D, was lacking, however the majority of the group favoured combination therapy with ezetimibe and the addition **of PCSK9 inhibitors** in high-risk patients. PMID: 28434484
REFERENCE: *Laufs U et al, for the SAMS expert working group. Practical aspects in the management of statin-associated muscle symptoms (SAMS). Atheroscler Suppl. 2017 Apr;26:45-55.*

With regard to vitamin D deficiency, several studies (estimated to be of low quality due to study designs) have suggested an association between vitamin D deficiency and SAMS

- Ovesjö ML et al. Low Vitamin D Levels and Genetic Polymorphism in the Vitamin D Receptor are Associated with Increased Risk of Statin-Induced Myopathy. Basic Clin Pharmacol Toxicol. 2016 Mar;118(3):214-8.
- Pereda CA et al. Is there really a relationship between serum vitamin D (25OHD) levels and the musculoskeletal pain associated with statin intake? A systematic review. Reumatol Clin. 2016 Nov - Dec;12(6):331-335.
- Palamaner Subash Shantha G et al. Association of vitamin D and incident statin induced myalgia--a retrospective cohort study. PLoS One. 2014 Feb 19;9(2):e88877.

Note that the ACC and AHA have a "Statin Intolerance App" to guides "clinicians through the process of managing and treating patients who report muscle symptoms while on statin therapy". According to the ACC "The app facilitates and adds structure to the clinician-patient discussion and includes questions to evaluate muscle-related symptoms, step-by-step guidance in the management of statin-related muscle symptoms, and a drug comparison tool for consideration of statin characteristics and potential drug–drug interactions."

Non-Statin Therapies

The inflammatory hypothesis of atherosclerosis generation is not new. According to Harrington (N Engl J Med. 2017 Sep 21;377(12):1197-1198), “Inflammatory cells and signals drive the healing response to vascular injury, allowing the initiation and growth of atherosclerotic plaque. Inflammatory reactions probably increase plaque instability, possibly resulting in plaque rupture, fissuring, or erosion and setting up the substrate for the thrombotic response that causes myocardial damage or infarction.” “Canakinumab, a human monoclonal antibody against interleukin-1β (a cytokine central to the inflammatory process), is approved for use in systemic juvenile idiopathic arthritis and cryopyrin-associated periodic syndromes.” The following abstract demonstrates that Canakinumab showed modest benefits in patients with established CV disease and an elevated hsCRP (lower rates of non-fatal MI, but no difference in all-cause mortality), but was also associated with harm signals (higher rates of fatal infections) and some unexplained results (lower cancer death rates). The cost is ~ $65,000 annually.

7. Anti-inflammatory therapy with canakinumab associated with reduced CV event rates

BACKGROUND: Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.
METHODS: We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.
RESULTS: At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group. The hazard ratios as compared with placebo were as follows: in the 50-mg group, 0.93 (95% confidence interval [CI], 0.80 to 1.07; P=0.30); in the 150-mg group, 0.85 (95% CI, 0.74 to 0.98; P=0.021); and in the 300-mg group, 0.86 (95% CI, 0.75 to 0.99; P=0.031). The 150-mg dose, but not the other doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P=0.005). Canakinumab was associated with a higher incidence of fatal infection than was placebo. There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P=0.31).
CONCLUSIONS: Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering. (Funded by Novartis; CANTOS ClinicalTrials.gov number, NCT01327846.)
***REFERENCE**: Ridker PM, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017 Sep 21;377(12):1119-1131.*

8. HDL modifying drug has a small effect on CV events, no effect on mortality

Clinical question: Does the cholesteryl ester transfer protein inhibitor anacetrapib improve outcomes in patients with known vascular disease and a low LDL level who are already taking a statin?
Study design: Randomized controlled trial (double-blinded)
Funding source: Industry
Allocation: Uncertain
Setting: Outpatient (any)
Synopsis: Previous studies of CETP inhibitors have not shown any clinical benefit, and some have shown net harm. Anacetrapib is a CETP inhibitor that has been shown to be relatively safe in previous studies, although no benefit was seen in smaller trials of patients at high risk for CV disease. The current study enrolled 30,449 persons 50 years and older with known vascular disease (88% coronary heart disease, 22% cerebrovascular disease, 8% peripheral vascular disease) and gave them atorvastatin to achieve an LDL cholesterol level of less than 77 mg/dL (2 mmol/L) and a total cholesterol level of less than 155 mg/dL (4 mmol/L). They were then randomized to receive anacetrapib 100 mg once daily or matching placebo. The groups were balanced at baseline, with a mean age of 68 years, a mean LDL of 61 mg/dL while taking a statin, and a mean high-density lipoprotein (HDL) of 40 mg/dL. Follow-up was excellent over a median of 4.1 years. As expected, patients in the intervention group had a lower mean LDL level (38 vs 65 mg/dL) and a higher HDL level (85 vs 42 mg/dL). There was no efffect on all-cause mortality, CV mortality, incidence of cancer, or non-CV mortality.There was a small decrease in the primary combined outcome of CV death, myocardial infarction, and revascularization (10.8% vs 11.8%; P = .004; NNT = 100), primarily due to a decrease in the risk of myocardial infarction (4.4% vs 5.1%; P = .007; NNT = 143 over 4.1 years). The risk of any major vascular event was also slightly lower (13.6% vs 14.5%; P = .02; NNT = 111 over 4.1 years).

The drug was well tolerated.
Bottom line: In patients with known cardiovascular (CV) disease who are taking a statin, adding the cholesteryl ester transfer protein (CETP) inhibitor anacetrapib has no effect on mortality but slightly reduces the likelihood of a major vascular event (number needed to treat [NNT] = 111 over 4.1 years). If the drug costs US$300 per month (it is not yet available), it would cost approximately US$1.6 million to prevent that one event. (LOE = 1b)
Reference: *The HPS3/TIMI55REVEAL Collaborative Group, Bowman L, Hopewell JC, et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 2017;377(13):1217-1227.*

According to a new release, “Merck will not be seeking approval for anacetrapib, its cholesteryl ester transfer protein (CETP) inhibitor aimed at raising HDL cholesterol levels. The company joins several others that have abandoned development of drugs in this class owing to lack of efficacy or safety.”

According to Dr. Harlan Krumholz, "The saga of this drug class is a cautionary tale; once thought of as the path toward extinguishing heart disease because of its remarkable effect on lipids, the story ends with a whimper and lessons about the need to validate surrogate outcomes."

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

Proprotein convertase subtilisin/kexin type 9 represents primarily a hepatocyte enzyme whose function includes regulating the number of low-density lipoprotein receptor (LDL-R) on hepatocytes. Briefly, when the LDL-R is complexed to an LDL particle, are both degraded in a lysosome. Inhibition of PCSK9 increases LDL-R “recycling” effectively increasing the number of LDL-R receptors on hepatocytes. The PCSK9 enzyme activity has been found to be correlated with CV disease, and **inhibition of PCSK9** is associated with **lower circulating LDL levels** (average LDL reduction of 58%).

PCSK9 inhibitors are monoclonal antibodies (with the potential for limited drug-drug interactions and ADEs). Currently there are 2 PCSK9 inhibitors (alirocumab | Praulent® and evolocumab | Repatha®) each administered subcutaneously once or twice monthly. Interesting, according to Noel and Beavers, both are also being studied in patients with HIV and in patients with DM. In addition to the cost (~$14000/year), and potential concern is a correlation of neurocognitive impairment (amnesia and delirium) and use of PCSK9 inhibitors.

In 2015 2 studies of these agents were published when *added to maximally tolerated statin therapy*. Evolocumab was associated with a decreased need for coronary revascularization (0.5% vs 1.1%, and TIA 0% vs 0.3%) but higher rates of discontinuation due to ADE (NNH 44). (N Engl J Med 2015;372(16):1500-1509). Alirocumab was associated with a decreased rate of non-fatal MI (0.9% vs 2.3%) but higher ADE (NNH = 27)

9. PCSK9 inhibitors | little or no effect on mortality

BACKGROUND: Despite the availability of effective drug therapies that reduce low-density lipoprotein (LDL)-cholesterol (LDL-C), cardiovascular disease (CVD) remains an important cause of mortality and morbidity. Therefore, additional LDL-C reduction may be warranted, especially for patients who are unresponsive to, or unable to take, existing LDL-C-reducing therapies. By inhibiting the proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme, monoclonal antibodies (PCSK9 inhibitors) may further reduce LDL-C, potentially reducing CVD risk as well.
OBJECTIVES: Primary To quantify short-term (24 weeks), medium-term (one year), and long-term (five years) effects of PCSK9 inhibitors on lipid parameters and on the incidence of CVD. Secondary To quantify the safety of PCSK9 inhibitors, with specific focus on the incidence of type 2 diabetes, cognitive function, and cancer. Additionally, to determine if specific patient subgroups were more or less likely to benefit from the use of PCSK9 inhibitors.
SEARCH METHODS: We identified studies by systematically searching the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and Web of Science. We also searched Clinicaltrials.gov and the International Clinical Trials Registry Platform and screened the reference lists of included studies. We identified the studies included in this review through electronic literature searches conducted up to May 2016 and added three large trials published in March 2017.

SELECTION CRITERIA: All parallel-group and factorial randomised controlled trials (RCTs) with a follow-up time of at least 24 weeks were eligible.
DATA COLLECTION AND ANALYSIS: Two review authors independently reviewed and extracted data. When data were available, we calculated pooled effect estimates.
MAIN RESULTS: We included 20 studies with data on 67,237 participants (median age 61 years; range 52 to 64 years). Twelve trials randomised participants to alirocumab, three trials to bococizumab, one to RG7652, and four to evolocumab.Owing to the small number of trials using agents other than alirocumab, we did not differentiate between types of PCSK9 inhibitors used. We compared PCSK9 inhibitors with placebo (thirteen RCTs), ezetimibe (two RCTs) or ezetimibe and statins (five RCTs).Compared with placebo, PCSK9 inhibitors decreased LDL-C by 53.86% (95% confidence interval (CI) 58.64 to 49.08; eight studies; 4782 participants; GRADE: moderate) at 24 weeks; compared with ezetimibe, PCSK9 inhibitors decreased LDL-C by 30.20% (95% CI 34.18 to 26.23; two studies; 823 participants; GRADE: moderate), and compared with ezetimibe and statins, PCSK9 inhibitors decreased LDL-C by 39.20% (95% CI 56.15 to 22.26; five studies; 5376 participants; GRADE: moderate).Compared with placebo, PCSK9 inhibitors decreased the risk of CVD events, with a risk difference (RD) of 0.91% (odds ratio (OR) of 0.86, 95% CI 0.80 to 0.92; eight studies; 59,294 participants; GRADE: moderate). Compared with ezetimibe and statins, PCSK9 inhibitors appeared to have a stronger protective effect on CVD risk, although with considerable uncertainty (RD 1.06%, OR 0.45, 95% CI 0.27 to 0.75; three studies; 4770 participants; GRADE: very low). No data were available for the ezetimibe only comparison. Compared with placebo, PCSK9 probably had little or no effect on mortality (RD 0.03%, OR 1.02, 95% CI 0.91 to 1.14; 12 studies; 60,684 participants; GRADE: moderate). Compared with placebo, PCSK9 inhibitors increased the risk of any adverse events (RD 1.54%, OR 1.08, 95% CI 1.04 to 1.12; 13 studies; 54,204 participants; GRADE: low). Similar effects were observed for the comparison of ezetimibe and statins: RD 3.70%, OR 1.18, 95% CI 1.05 to 1.34; four studies; 5376 participants; GRADE: low. Clinical event data were unavailable for the ezetimibe only comparison.
AUTHORS' CONCLUSIONS: Over short-term to medium-term follow-up, PCSK9 inhibitors reduced LDL-C. Studies with medium-term follow-up time (longest median follow-up recorded was 26 months) reported that PCSK9 inhibitors (compared with placebo) decreased CVD risk but may have increased the risk of any adverse events (driven by SPIRE-1 and -2 trials). Available evidence suggests that PCSK9 inhibitor use probably leads to little or no difference in mortality. Evidence on relative efficacy and safety when PCSK9 inhibitors were compared with active treatments was of low to very low quality (GRADE); follow-up times were short and events were few. Large trials with longer follow-up are needed to evaluate PCSK9 inhibitors versus active treatments as well as placebo. Owing to the predominant inclusion of high-risk patients in these studies, applicability of results to primary prevention is limited. Finally, estimated risk differences indicate that PCSK9 inhibitors only modestly change absolute risks (often to less than 1%).
***REFERENCE**: Schmidt AF et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017 Apr 28;4:CD011748.*

In abstract #10, 27,564 patients with atherosclerotic cardiovascular disease (i.e. MI, thrombotic CVA within 5 years, symptomatic PAD) PLUS 1 major risk factor or 2 minor risk factors and LDL levels at or above 70 mg/dL who were given evolocumab plus statin (99% were on moderate or high-intensity statins) had a significantly lower rate of the composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, and coronary revascularization, compared with patients given placebo plus a statin after 2 years' follow-up (9.8% vs. 11.3%). The mean percentage reduction of LDL vs placebo was 59% (mean baseline LDL 92 to 30 mg/dL). No significant differences were noted in ADE vs placebo (including neurocognitive effects). The log-term safety of LDL cholesterols of ~ 30 mg/dL are not known.

10. Evolocumab + a statin ↓ MACE rates more than placebo + a statin

BACKGROUND: Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.
METHODS: We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70 mg per deciliter (1.8 mmol per liter) or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.
RESULTS: At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).
CONCLUSIONS: In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

***REFERENCE**: Sabatine MS, et al FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-1722.*

Evolocumab previously approved for use in adults with heterozygous familial hypercholesterolemia, homozygous familial hypercholesterolemia, or clinical atherosclerotic cardiovascular disease whose LDL levels were still high despite other treatments has a new FDA approved indication, the prevention of cardiovascular events (e.g., myocardial infarction, stroke, coronary revascularization) in patients with existing cardiovascular disease.

The annual cost of alirocumab and evolocumab is approximately $14,000. Cost analyses suggest a price reduction of approximately 60% to ~ $5,000/yr for the agents to be considered cost-effective. Note that In Nov 2016 Pfizer announced that it was discontinuing the development progrma for another PCSK9 inhibitors (bococizumab) noting that "....is not likely to provide value to patients, physicians, or shareholders."

11. PCSK9 inhibitors associated with ↑↑↑↑ Cost

Importance: Preliminary cost-effectiveness analyses of proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) were based on benefits estimated from reductions in low-density lipoprotein cholesterol that occurred in PCSK9i trials with variable results. The recent Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial provides better information about the effectiveness of the drug.
Objective: To use the trial results to determine the cost-effectiveness of a PCSK9i and statin treatment strategy compared with a statin alone strategy.
Design, Setting, and Participants: We derived observed rates of events, outcomes, cost of care, and health insurance from existing literature for a theoretical cohort of patients designed to resemble the FOURIER PCSK9i trial population and created a Markov model during the time horizon of a full lifetime.
Main Outcomes and Measures: We evaluated the incremental cost-effectiveness ratio from a health system perspective, and the return on investment from a private payer perspective. For both measures, we assumed an annual PCSK9i drug price of $14 300, with a lapse in US patent protection that would reduce the price by 43% in year 12. Costs were reported in 2016 US dollars.
Results: This study modeled 1000 hypothetical patients with attributes similar to those of the FOURIER trial cohort. At the current price, the incremental cost-effectiveness ratio of statin plus PCSK9i therapy was $337 729 per quality-adjusted life-year. Our probabilistic sensitivity analysis found that a statin plus PCSK9i strategy had a low probability (<1%) of being cost effective at the commonly accepted societal threshold of $100 000 per quality-adjusted life-year. Furthermore, PCSK9i produced a negative return on investment of 86% for private payers. In our threshold analysis, the price of PCSK9i would need to drop 62%, to $5459 per year, to reach $100 000 per quality-adjusted life year.
Conclusions and Relevance: At current prices, the addition of PCSK9i to statin therapy is estimated to provide an additional quality-adjusted life year for $337 729. Significant discounts are necessary to meet conventional cost-effectiveness standards.
***Reference**: Arrieta A et al. Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers: Insights Derived From the FOURIER Trial. JAMA Cardiol. 2017 Dec 1;2(12):1369-1374.*

12: Adding ezetimibe to moderate-dose statin reduces nonfatal MI only (NNT = 58 for 6 years)

Clinical question: Is ezetimibe plus simvastatin 40 mg more effective than simvastatin 40 mg alone after an episode of acute coronary syndrome?
Study design: Randomized controlled trial (double-blinded)
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: These researchers identified adults 50 years and older who had been hospitalized for acute coronary syndrome in the previous 10 days who had a low-density lipoprotein level greater than 50 mg/dL (1.3 mmol/L) and less than 100 mg/dL (2.6 mmol/L) if already taking a statin or less than 125 mg/dL (3.2 mmol/L) if not using long-term statin therapy. The patients' mean age was 64 years, 76% were men, 84% were white, 27% had diabetes, and 70% had undergone a percutaneous coronary intervention during their episode of acute coronary syndrome. The patients were randomized to receive either simvastatin 40 mg once daily or simvastatin 40 mg once daily plus ezetimibe 10 mg once daily. Groups were balanced at the beginning of the study, with slightly more than 9000 in each group, and analysis was by intention to treat. Patients were followed up for at least 2.5 years, with a median follow-up of 6 years; the authors note that the study protocol was modified 5 times, including an increase in the sample size (presumably because they weren't finding a difference that was statistically significant with the original sample size). It took a while, but after approximately 3 to 4 years they began to see a difference between groups, ultimately a 2.0% reduction in the likelihood of a composite outcome of cardiovascular death, myocardial infarction, or stroke (32.7% vs 34.7%; P = .02; number needed to treat [NNT] = 50 for 6 years). However, the individual end points of all-cause mortality, cardiovascular death, or fatal myocardial infarction were nearly identical between groups. Most of the improvement in the composite outcome came from a reduction in nonfatal MI (13.1% vs 14.8%; P = .002; NNT = 58). There was also a small reduction in the risk of stroke (4.2% vs 4.8%; P = .05; NNT = 167 for 6 years).
Bottom line: Patients with known heart disease should have high-intensity statin therapy, so the comparison group in this study

actually received less than the recommended dose of a statin. Those receiving ezetimibe plus simvastatin had a marginally better outcome: 1 fewer nonfatal myocardial infarction for every 58 patients who added ezetimibe for 6 years after an acute coronary syndrome. At best, this suggests that simvastatin plus ezetimibe may be an alternative to high-intensity statin therapy for patients who do not tolerate the latter.

Reference: *Cannon CP, Blazing MA, Giugliano RP, et al, for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-2397*

2017 ACC update on use of non-statin therapies for LDL-C lowering

In 2017, the ACC published a 38 page "focused update" called an Expert Consensus Decision Pathway (ECDP) on the "Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk" mostly to accommodate the expanded use of PCSK9 Inhibition and ezetimibe in patients with clinical ASCVD already on statin therapy for secondary prevention. Only 4 pages of COI declarations are provided in this document (in small font).

The ACC is clear that this is not an evidence-based document and in the development of the ECDP, "… this process did not involve formal systematic reviews, grading of evidence, or synthesis of evidence."

My brief synopsis of this ECDP includes:

Continued - ish endorsement the four evidence based statin-benefit groups:

1. Patients ≥ 21 years with stable clinical ASCVD;
    a) Without comorbidities
    b) With comorbidities (see below***)
    c) With baseline LDL-C > 190 mg/dL not due to secondary causes
2. Patients with LDL-C > 190 mg/dL, not due to secondary causes;
3. Patients aged 40 to 75 years with diabetes mellitus and LDL-C 70 - 189 mg/dL
4. Patients aged 40 to 75 years with no diabetes, but with LDL-C 70 to 189 mg/dL and predicted 10-year ASCVD risk >7.5%.

BUT they are now emphasizing both relative and absolute LDL "targets" – a point mentioned but not emphasized (in my opinion) in the 2013 guidelines. The 2017 document states, "these are not firm triggers" but factors that may be considered within the broader context of an individual patient's clinical situation."

Indicators of *efficacy* are the following targets:

- **50% LDL-C reduction** from baseline for high-intensity statin doses
- **30% to <50% LDL-C reduction** from baseline for moderate-intensity statin doses

Note that if you do not have baseline (non-treatment) LDL data, then the ACC gives tacit endorsement to using the absolute LDL level of 70 mg/dL for a high-intensity statin target or 100mg/dL for a moderate-intensity statin target. Note the strategy of "treating to target" (and these levels specifically) were not endorsed in the 2013 guideline.

If patients in the above 4 groups are not at target AND they are a) adherent, b) **on high-intensity statin**, c) engaged in lifestyle modification (including phytosterol use), then after shared decision making ….

For group 1a

- Consider ezetimibe first
- Consider PCSK9 inhibitors second (mostly if fully statin intolerant, and attempts to ↓ LDL with ezetimibe or bile acid sequestrants do not reach LDL targets)

For groups 1b, 1c and 2:

- Consider ezetimibe or PCSK9 inhibitors as initial non-statin therapies

For groups 3 and 4:

- Consider ezetimibe (or bile acid sequestrants if ezetimibe intolerant and TG's < 300mg/dL) – there is no recommendation at all for PCSK9 inhibitors in these groups

13: AHA consensus decision pathway on non-statin therapies for LDL-C

In 2016, the American College of Cardiology published the first expert consensus decision pathway (ECDP) on the role of non-statin therapies for low-density lipoprotein (LDL)-cholesterol lowering in the management of atherosclerotic cardiovascular disease (ASCVD) risk. Since the publication of that document, additional evidence and perspectives have emerged from randomized clinical trials and other sources, particularly considering the longer-term efficacy and safety of proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors in secondary prevention of ASCVD. Most notably, the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial and SPIRE-1 and -2 (Studies of PCSK9 Inhibition and the Reduction of Vascular Events), assessing evolocumab and bococizumab, respectively, have published final results of cardiovascular outcomes trials in patients with clinical ASCVD and in a smaller number of high-risk primary prevention patients. In addition, further evidence on the types of patients most likely to benefit from the use of ezetimibe in addition to statin therapy after acute coronary syndrome has been published. Based on results from these important analyses, the ECDP writing committee judged that it would be desirable to provide a focused update to help guide clinicians more clearly on decision making regarding the use of ezetimibe and PCSK9 inhibitors in patients with clinical ASCVD with or without comorbidities. In the following summary table, changes from the 2016 ECDP to the 2017 ECDP Focused Update are highlighted, and a brief rationale is provided. The content of the full document has been changed accordingly, with more extensive and detailed guidance regarding decision making provided both in the text and in the updated algorithms. Revised recommendations are provided for patients with clinical ASCVD with or without comorbidities on statin therapy for secondary prevention. The ECDP writing committee judged that these new data did not warrant changes to the decision pathways and algorithms regarding the use of ezetimibe or PCSK9 inhibitors in primary prevention patients with LDL-C <190 mg/dL with or without diabetes mellitus or patients without ASCVD and LDL-C ≥190 mg/dL not due to secondary causes. Based on feedback and further deliberation, the ECDP writing committee down-graded recommendations regarding bile acid sequestrant use, recommending bile acid sequestrants only as optional secondary agents for consideration in patients intolerant to ezetimibe. For clarification, the writing committee has also included new information on diagnostic categories of heterozygous and homozygous familial hypercholesterolemia, based on clinical criteria with and without genetic testing. Other changes to the original document were kept to a minimum to provide consistent guidance to clinicians, unless there was a compelling reason or new evidence, in which case justification is provided.
***Reference**: Lloyd-Jones DM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017 Oct 3;70(14):1785-1822.*

Triglycerides

BACKGROUND: Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.
METHODS: We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.
RESULTS: A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter

(3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).
CONCLUSIONS: Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361 .).
***REFERENCE**: Bhatt DL for the REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812792.*

Conclusions

- The USPSTF recommend statin use in adults aged 40 -75 with >1 CV risk factor and 10 year calculated CV risk of > 10%
- Evidence for improved CV outcomes with statins in older adults is lacking
- Major guidelines on statin therapy differ from each other (some substantially)
- Non-fasting lipid profiles are accurate
- Several recommendations exist for Statin Associated Muscle Symptoms (SAMS) and an online application exists to guide clinician managing SAMS
- A host of non-statin therapies exist for dyslipidemia, and in 2017 the ACC and AHA published an Expert Consensus Decision Pathway (ECDP) on when to consider ezetimibe or PCSK9 inhibitors
- IN patients with established ASCVD the use of 2 g of icosapent ethyl (Vacepa®) twice daily was associated with lower MACE rates after 4.9 years

Appendix

Phytosterols

Consider phytosterols and/or soluble dietary fibre. The FDA- approved claims for these are:

For phytosterols:

> "Foods containing at least 0.65 g per serving of plant sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, *may reduce the risk of heart disease*.

For plant stanol esters:

> "Foods containing at least 1.7 g per serving of plant stanol esters, eaten twice a day with meals for a total daily intake of at least 3.4 g, as part of a diet low in saturated fat and cholesterol, *may reduce the risk of heart disease*."

For soluble dietary fibre:

> "Soluble fiber as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease"

Note also that the USDA in 2015 stated, "Dietary cholesterol is no longer a nutrient of concern"

I do not know much about a phytosterol diet, so here is a link to the Cleveland Clinic on this topic.

Comorbidities

***Comorbidities to consider in management decisions include (almost everyone with CAD!):

- DM
- Recent (< 3 months) ASCVD event
- ASCVD event while on a statin
- Poorly controlled other major ASCVD risk factors
- Elevated Lp(a)
- CKD
- CHF (symptomatic)
- Maintenance hemodialysis
- Baseline LDL > 190 mg/dLnot due to a secondary cause
- Age > 65
- Prior MI
- Prior nonhemorragic CVA
- Current smoking
- Symptomatic PAD with prior hx of MI or CVA
- Hx coronary revascularization
- Residual CAD with > 40% stenosis in > 2 large vessels
- HDL < 40 for men or < 50 for women
- Hs-CRP > 2 mg/L
- Metabolic syndrome

Ezetimibe

Mechanism of action: Reduces cholesterol absorption in small intestine.
Mean % reduction in LDL-C: Monotherapy—18%; combination therapy with statin (incremental reduction)—25%
Adverse effects: Monotherapy—upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity; combination with statin—nasopharyngitis, myalgia, upper respiratory tract infection, arthralgia, diarrhea. However, generally well tolerated
Cost: Generic available | goodrx.com (January 28, 2018) #30 10-mg tablets cost ~ $12

Dementia/End-of- Life Care Gary Ferenchick MD

Objectives

1. Recognize that mild cognitive impairment normalizes over time in a large percentage of patients
2. Anti-cholinergic medication use is associated with dementia
3. PPIs are not associated with dementia
4. The general conclusions from 2 major reports on dementia published in 2017
5. The evidence for cognitive training, medications/OTCs, and physical activity for preventing dementia is insufficient
6. Advanced care planning (ACP) occurs more commonly with an easy to use interactive web site
7. Percutaneous endoscopic gastrostomy (PEG) tube use does not improve any outcome in patients with dementia
8. Melatonin may help improve sleep in patients with dementia

Dementia represents a decline from a previously attained cognitive level AND affects activities of daily living or social functioning
Mild cognitive impairment (MCI) represents a decline from a previously attained cognitive level, but the individual can still engage in complex activities (e.g paying bills, taking meds)

MCI is described as an intermediate phase between normal cognition and dementia; it is associated with an objective deficit and cognitive abilities but does not yet affect the patient's functional independence. MCI is considered a relevant risk factor for the development of dementia. However, the first abstract notes a substantial percentage of patients with MCI normalize over time

1. Mild cognitive impairment (MCI) appears reversible

BACKGROUND: Although mild cognitive impairment often precedes dementia, it can also resolve spontaneously.
METHODS: These Italian and French authors performed a systematic review and meta-analysis to determine the proportion of subjects who revert from mild cognitive impairment to normal cognition. A literature search for 1999-2015 identified 25 longitudinal studies on 6914 patients with mild cognitive impairment (mean age 75; 51% female) who had at least two-year follow-up. The primary outcome was the percentage of patients who reverted to normal cognition.
RESULTS: Subjects were derived from population cohorts (15 studies; mean 3.9 years of follow-up) or clinical settings (10 studies; 3.2 years of follow-up). Reversion from mild cognitive impairment to normal cognition occurred in 1243 subjects overall (18%; 95% CI, 14-22%), with high heterogeneity (I^2=96.1%; $p<0.001$). Meta-regression showed a significant association between effect size and study setting, whereby the reversion rate was 8% (95% CI, 4-11%) in clinical settings and 25% (95% CI, 19-30%) in population cohorts. When only high-quality studies were included, the reversion rate was 26%. Reversion rates did not depend on participant age or duration of follow-up. Reasons for the discrepant results were hypothesized to include mis-classification of subjects, wide variation in definitions of mild cognitive impairment, and the unstable and fluctuating nature of MCI.
CONCLUSIONS: Mild cognitive impairment appears to normalize over time in a fairly large percentage of patients, and thus should not be considered as the first manifestation of dementia. Physicians must be aware of the bidirectionality of cognitive impairment to avoid overdiagnosis and overtreatment. 52 references (marco.canevelli@gmail.com – no reprints)
***REFERENCE**: Canevelli, M., et al. SPONTANEOUS REVERSION OF MILD COGNITIVE IMPAIRMENT TO NORMAL COGNITION: A SYSTEMATIC REVIEW OF LITERATURE AND META-ANALYSIS. J Am Med Dir Assoc 17(10):943, October 1, 2016*

Factors associated (or not) with dementia

2. Anticholinergic medication use associated with dementia risk

IMPORTANCE: Many medications have anticholinergic effects. In general, anticholinergic-induced cognitive impairment is considered reversible on discontinuation of anticholinergic therapy. However, a few studies suggest that anticholinergics may be associated with an increased risk for dementia.
OBJECTIVE: To examine whether cumulative anticholinergic use is associated with a higher risk for incident dementia.
DESIGN, SETTING, AND PARTICIPANTS: Prospective population-based cohort study using data from the Adult Changes in Thought study in Group Health, an integrated health care delivery system in Seattle, Washington. We included 3434 participants 65 years or

older with no dementia at study entry. Initial recruitment occurred from 1994 through 1996 and from 2000 through 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants were followed up every 2 years. Data through September 30, 2012, were included in these analyses.
EXPOSURES: Computerized pharmacy dispensing data were used to ascertain cumulative anticholinergic exposure, which was defined as the total standardized daily doses (TSDDs) dispensed in the past 10 years. The most recent 12 months of use was excluded to avoid use related to prodromal symptoms. Cumulative exposure was updated as participants were followed up over time.
MAIN OUTCOMES AND MEASURES: Incident dementia and Alzheimer disease using standard diagnostic criteria. Statistical analysis used Cox proportional hazards regression models adjusted for demographic characteristics, health behaviors, and health status, including comorbidities.
RESULTS: The most common anticholinergic classes used were tricyclic antidepressants, first-generation antihistamines, and bladder antimuscarinics. During a mean follow-up of 7.3 years, 797 participants (23.2%) developed dementia (637 of these [79.9%] developed Alzheimer disease). A 10-year cumulative dose-response relationship was observed for dementia and Alzheimer disease (test for trend, P < .001). For dementia, adjusted hazard ratios for cumulative anticholinergic use compared with nonuse were 0.92 (95% CI, 0.74-1.16) for TSDDs of 1 to 90; 1.19 (95% CI, 0.94-1.51) for TSDDs of 91 to 365; 1.23 (95% CI, 0.94-1.62) for TSDDs of 366 to 1095; and 1.54 (95% CI, 1.21-1.96) for TSDDs greater than 1095. A similar pattern of results was noted for Alzheimer disease.
Results were robust in secondary, sensitivity, and post hoc analyses.
CONCLUSIONS AND RELEVANCE: Higher cumulative anticholinergic use is associated with an increased risk for dementia. Efforts to increase awareness among health care professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.
REFERENCE: *Gray SL et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015 Mar;175(3):401-7.*

Medications associated with dementia in this study included: antihistamines, antidepressants (amitriptyline, paroxetine), antiemetic (meclizine, prochlorperazine), antiparkinsons agents (benztropine); antipsychotics (olanzapine), bladder antimuscarinics (oxybutynin, tolteradine), skeletal muscle relaxants (cyclobenzaprine), GI antispasmodics (hyocyamine, scopolamine)

3. No association between PPIs and Dementia

OBJECTIVES: The objective of the study was to investigate whether proton pump inhibitor (PPI) use is associated with an increased risk of clinically verified Alzheimer's disease (AD).
METHODS: A Finnish nationwide nested case-control study MEDALZ includes all community-dwelling individuals with newly diagnosed AD during 2005-2011 (N=70,718), and up to four age-, sex-, and region of residence-matched comparison individuals for each case (N=282,858). Data were extracted from Finnish nationwide health-care registers. PPI use was derived from purchases recorded in the Prescription register data since 1995 and modeled to drug use periods with PRE2DUP method. AD was the outcome measure.
RESULTS: PPI use was not associated with risk of AD with 3-year lag window applied between exposure and outcome (adjusted odds ratio (OR) 1.03, 95% confidence interval (CI) 1.00-1.05). Similarly, longer duration of use was not associated with risk of AD (1-3 years of use, adjusted OR 1.01 (95% CI 0.97-1.06); ≥3 years of use adjusted OR 0.99 (95% CI 0.94-1.04)). Higher dose use was not associated with an increased risk (≥1.5 defined daily doses per day, adjusted OR 1.03 (95% CI 0.92-1.14)).
CONCLUSIONS: In conclusion, we found no clinically meaningful association between PPI use and risk of AD. The results for longer duration of cumulative use or use with higher doses did not indicate dose-response relationship.
REFERENCE*: Taipale H et al. No Association Between Proton Pump Inhibitor Use and Risk of Alzheimer's Disease. Am J Gastroenterol. 2017 Jul 11. doi: 10.1038/ajg.2017.196.*

4. No association between PPIs and Dementia (again)

OBJECTIVES: To examine the risk associated with the use of proton pump inhibitors (PPIs) of conversion to mild cognitive impairment (MCI), dementia, and specifically Alzheimer's disease (AD).
DESIGN: Observational, longitudinal study.
SETTING: Tertiary academic Alzheimer's Disease Centers funded by the National Institute on Aging.
PARTICIPANTS: Research volunteers aged 50 and older with two to six annual visits; 884 were taking PPIs at every visit, 1,925 took PPIs intermittently, and 7,677 never reported taking PPIs. All had baseline normal cognition or MCI.
MEASUREMENTS: Multivariable Cox regression analyses evaluated the association between PPI use and annual conversion of baseline normal cognition to MCI or dementia or annual conversion of baseline MCI to dementia, controlling for demographic characteristics, vascular comorbidities, mood, and use of anticholinergics and histamine-2 receptor antagonists.
RESULTS: Continuous (always vs never) PPI use was associated with lower risk of decline in cognitive function (hazard ratio (HR) = 0.78, 95% confidence interval (CI) =0.66-0.93, P = .005) and lower risk of conversion to MCI or AD (HR = 0.82, 95% CI = 0.69-0.98, P = .03). Intermittent use was also associated with lower risk of decline in cognitive function (HR = 0.84, 95% CI = 0.76-0.93, P = .001) and risk of conversion to MCI or AD (HR = 0.82, 95% CI = 0.74-0.91, P = .001). This lower risk was found for persons with normal cognition or MCI.
CONCLUSION: Proton pump inhibitors were not associated with greater risk of dementia or of AD, in contrast to recent reports. Study limitations include reliance on self-reported PPI use and lack of dispensing data. Prospective studies are needed to confirm these results to guide empirically based clinical treatment recommendations.

REFERENCE: *Goldstein FC et al. Proton Pump Inhibitors and Risk of Mild Cognitive Impairment and Dementia. J Am Geriatr Soc. 2017 Sep;65(9):1969-1974.*

Lancet Commission and the AHA/ASA 2017 reports

In 2017 2 large reports related to dementia were published

- Defining Optimal Brain Health in Adults by the American Heart Association and American Stroke Association
- Lancet Commission Report on "Dementia prevention, intervention and care"

5. Defining optimal brain health in adults: AHA/ASA advisory

Cognitive function is an important component of aging and predicts quality of life, functional independence, and risk of institutionalization. Advances in our understanding of the role of cardiovascular risks have shown them to be closely associated with cognitive impairment and dementia. Because many cardiovascular risks are modifiable, it may be possible to maintain brain health and to prevent dementia in later life. The purpose of this American Heart Association (AHA)/American Stroke Association presidential advisory is to provide an initial definition of optimal brain health in adults and guidance on how to maintain brain health. We identify metrics to define optimal brain health in adults based on inclusion of factors that could be measured, monitored, and modified. From these practical considerations, we identified 7 metrics to define optimal brain health in adults that originated from AHA's Life's Simple 7: 4 ideal health behaviors (nonsmoking, physical activity at goal levels, healthy diet consistent with current guideline levels, and body mass index <25 kg/m2) and 3 ideal health factors (untreated blood pressure <120/<80 mm Hg, untreated total cholesterol <200 mg/dL, and fasting blood glucose <100 mg/dL). In addition, in relation to maintenance of cognitive health, we recommend following previously published guidance from the AHA/American Stroke Association, Institute of Medicine, and Alzheimer's Association that incorporates control of cardiovascular risks and suggest social engagement and other related strategies. We define optimal brain health but recognize that the truly ideal circumstance may be uncommon because there is a continuum of brain health as demonstrated by AHA's Life's Simple 7. Therefore, there is opportunity to improve brain health through primordial prevention and other interventions. Furthermore, although cardiovascular risks align well with brain health, we acknowledge that other factors differing from those related to cardiovascular health may drive cognitive health. Defining optimal brain health in adults and its maintenance is consistent with the AHA's Strategic Impact Goal to improve cardiovascular health of all Americans by 20% and to reduce deaths resulting from cardiovascular disease and stroke by 20% by the year 2020. This work in defining optimal brain health in adults serves to provide the AHA/American Stroke Association with a foundation for a new strategic direction going forward in cardiovascular health promotion and disease prevention.
REFERENCE: *Gorelick PB et al. Defining Optimal Brain Health in Adults: A Presidential Advisory From the American Heart Association/American Stroke Association. Stroke. 2017 Oct;48(10):e284-e303.*

6. Lancet Commission Report

REFERENCE: Dementia prevention, intervention and care" (Livingston G et al. Dementia prevention, intervention, and care. Lancet. 2017 Dec 16;390(10113):2673-2734

The general theme of both documents is that that dementia has an important proportion of modifiable risk factors.

My major conclusions from the AHA/ASA document | the focus is primarily on CV risk reduction

- The definition of "optimal brain health" is optimal capacity to function adaptively in the environment.
    1. This could be assessed in terms of competencies across the domains of "thinking, moving, and feeling," encompassing, for example, the abilities pay attention, perceive, and recognize sensory input; to learn and remember; to communicate; to problem solve and make decisions; to have mobility; and to regulate emotional status.
    2. A healthy brain is one that can perform all the mental processes that encompass cognition such as the ability to learn and judge, use language, and remember
- Many brain disorders manifest later in life but, in fact, *are life-course illnesses*.
    1. Cumulative exposure to vascular risk factors throughout life, perhaps starting as early as in utero (and certainly from the fourth decade onward), affects the risk of … stroke and dementia

- Research has convincingly demonstrated that cardiovascular risk factors are major contributors to late-life cognitive health and risk of stroke and AD.
    1. Of all major cognitively impairing disorders, including AD, there is a vascular component in up to 80%.
    2. Cardiovascular risks are important targets for strategies to prevent or delay cognitive impairments and factors such as uncontrolled hypertension, diabetes mellitus, obesity, physical inactivity, smoking, and depression *are associated with compromised brain health*
- A strategy of using AHA Life's Simple 7 helps preserve cognition

    Health-Related Behaviors
    1. Nonsmoking status
    2. Physical activity at goal levels
    3. BMI <25 kg/m2
    4. Healthy diet consistent with current guidelines

    Health-Related Factors
    5. Untreated BP <120/<80 mm Hg
    6. Untreated total cholesterol <200 mg/dL
    7. Fasting blood glucose <100 mg/dL

7. Improvements in Life's Simple 7 associated with healthy vascular aging

Hypertension and increased vascular stiffness are viewed as inevitable parts of aging. To elucidate whether the age-related decrease in vascular function is avoidable, we assessed the prevalence, correlates, and prognosis of healthy vascular aging (HVA) in 3196 Framingham Study participants aged ≥50 years. We defined HVA as absence of hypertension and pulse wave velocity <7.6 m/s (mean+2 SD of a reference sample aged <30 years). Overall, 566 (17.7%) individuals had HVA, with prevalence decreasing from 30.3% in people aged 50 to 59 to 1% in those aged ≥70 years. In regression models adjusted for physical activity, caloric intake, and traditional cardiovascular disease (CVD) risk factors, we observed that lower age, female sex, lower body mass index, use of lipid-lowering drugs, and absence of diabetes mellitus were cross-sectionally associated with HVA (P<0.001 for all). A unit increase in a cardiovascular health score (Life's Simple 7) was associated with 1.55-fold (95% confidence interval, 1.38-1.74) age- and sex-adjusted odds of HVA. During a follow-up of 9.6 years, 391 CVD events occurred. In Cox regression models adjusted for traditional CVD risk factors, including blood pressure, HVA was associated with a hazard ratio of 0.45 (95% confidence interval, 0.26-0.77) for CVD relative to absence of HVA. Although HVA is achievable in individuals acculturated to a Western lifestyle, maintaining normal vascular function beyond 70 years of age is challenging. Although our data are observational, our findings support prevention strategies targeting modifiable factors and behaviors and obesity, in particular, to prevent or delay vascular aging and the associated risk of CVD.
REFERENCE: *Niiranen TJ et al. Prevalence, Correlates, and Prognosis of Healthy Vascular Aging in a Western Community-Dwelling Cohort: The Framingham Heart Study. Hypertension. 2017 Aug;70(2):267-274.*

Major conclusions from the Lancet document

35% of dementia is attributable to a combination of the following nine risk factors:

1. smoking
2. physical inactivity
3. midlife obesity
4. midlife hypertension
5. diabetes
6. education to a maximum of age 11–12 years
7. hearing loss
8. late life depression
9. social isolation

Conversely, completely eliminating the apolipoprotein E (ApoE) ε4 allele as the major *genetic risk factor* is calculated to produce a 7% reduction in incidence

Modifiable risk factors for dementia

The population attributable fraction (PAF) is the percentage reduction in new cases over a given time if a particular risk factor were eliminated.

According to the Lancet Commission report “The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER study) provided four intensive lifestyle-based strategies (diet, exercise, cognitive training, and vascular management) to more than 600 people who were older than 60 years and at high risk of dementia according to their age, sex, education, systolic blood pressure, total cholesterol, and physical activity. The study compared cognition in the intervention group versus controls who received general health advice. This highly intensive intervention consisted of about 200 meetings (300 h) with health professionals and trainers over 2 years. Participants in the intervention group showed a mean improvement versus the control group in a composite measure of cognition (d=0·13) on executive function and processing speed, but not memory. Despite the intervention’s intensity, the effect was small, although this outcome shows potential for lifestyle modification to improve cognitive function in people at risk of dementia. Pragmatic multimodal models for dementia prevention should be tested in other populations and

settings. Earlier intervention and longer followup will determine whether these approaches reduce dementia risk." (Abstract #8)

8: Multidomain interventions improve cognitive functioning in at-risk elderly people

BACKGROUND: Modifiable vascular and lifestyle-related risk factors have been associated with dementia risk in observational studies. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a proof-of-concept randomised controlled trial, we aimed to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population.
METHODS: In a double-blind randomised controlled trial we enrolled individuals aged 60-77 years recruited from previous national surveys. Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. We randomly assigned participants in a 1:1 ratio to a 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation. The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score. Analysis was by modified intention to treat (all participants with at least one post-baseline observation). This trial is registered at ClinicalTrials.gov, number NCT01041989.
FINDINGS: Between Sept 7, 2009, and Nov 24, 2011, we screened 2654 individuals and randomly assigned 1260 to the intervention group (n=631) or control group (n=629). 591 (94%) participants in the intervention group and 599 (95%) in the control group had at least one post-baseline assessment and were included in the modified intention-to-treat analysis. Estimated mean change in NTB total Z score at 2 years was 0·20 (SE 0·02, SD 0·51) in the intervention group and 0·16 (0·01, 0·51) in the control group. Between-group difference in the change of NTB total score per year was 0·022 (95% CI 0·002-0·042, p=0·030). 153 (12%) individuals dropped out overall. Adverse events occurred in 46 (7%) participants in the intervention group compared with six (1%) participants in the control group; the most common adverse event was musculoskeletal pain (32 [5%] individuals for intervention vs no individuals for control).
INTERPRETATION: Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.
***REFERENCE**: Ngandu T et al. A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015 Jun 6;385(9984):2255-63.*

9: Mediterranean diet is associated with improved cognitive function

IMPORTANCE: Oxidative stress and vascular impairment are believed to partly mediate age-related cognitive decline, a strong risk factor for development of dementia. Epidemiologic studies suggest that a Mediterranean diet, an antioxidant-rich cardioprotective dietary pattern, delays cognitive decline, but
clinical trial evidence is lacking.
OBJECTIVE: To investigate whether a Mediterranean diet supplemented with antioxidant-rich foods influences cognitive function compared with a control diet.
DESIGN, SETTING, AND PARTICIPANTS: Parallel-group randomized clinical trial of 447 cognitively healthy volunteers from Barcelona, Spain (233 women [52.1%]; mean age, 66.9 years), at high cardiovascular risk were enrolled into the Prevención con Dieta Mediterránea nutrition intervention trial from October 1, 2003, through December 31, 2009. All patients underwent neuropsychological assessment at inclusion and were offered retesting at the end of the study.
INTERVENTIONS: Participants were randomly assigned to a Mediterranean diet supplemented with extravirgin olive oil (1 L/wk), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat).
MAIN OUTCOMES AND MEASURES: Rates of cognitive change over time based on a neuropsychological test battery: Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Animals Semantic Fluency, Digit Span subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from the Wechsler Memory Scale, and the Color Trail Test. We used mean z scores of change in each test to construct 3 cognitive composites: memory, frontal (attention and executive function), and global.
RESULTS: Follow-up cognitive tests were available in 334 participants after intervention (median, 4.1 years). In multivariate analyses adjusted for confounders, participants allocated to a Mediterranean diet plus olive oil scored better on the RAVLT (P = .049) and Color Trail Test part 2 (P = .04) compared with controls; no between-group differences were observed for the other cognitive tests. Similarly adjusted cognitive composites (mean z scores with 95% CIs) for changes above baseline of the memory composite were 0.04 (-0.09 to 0.18) for the Mediterranean diet plus olive oil, 0.09 (-0.05 to 0.23; P = .04 vs controls) for the Mediterranean diet plus nuts, and -0.17 (-0.32 to -0.01) for the control diet. Respective changes from baseline of the frontal cognition composite were 0.23 (0.03 to 0.43; P = .003 vs controls), 0.03 (-0.25 to 0.31), and -0.33 (-0.57 to -0.09). Changes from baseline of the global cognition composite were 0.05 (-0.11 to 0.21; P = .005 vs controls) for the Mediterranean diet plus olive oil, -0.05 (-0.27 to 0.18) for the Mediterranean diet plus nuts, and -0.38 (-0.57 to -0.18) for the control diet. All cognitive composites significantly (P < .05) decreased from baseline in controls.
CONCLUSIONS AND RELEVANCE: In an older population, a Mediterranean diet supplemented with olive oil or nuts is associated with improved cognitive function.
TRIAL REGISTRATION: isrctn.org Identifier: ISRCTN35739639.
***REFERENCE**: Valls-Pedret C et al. Mediterranean Diet and Age-Related Cognitive Decline: A Randomized Clinical Trial. JAMA Intern Med. 2015 Jul;175(7):1094-103.*

Findings from RCTS on interventions to prevent Alzheimer disease and related dementias

The following four abstracts reflect the work of the Minnesota Evidence-based Practice Center (EPC) summarizing findings from RCTS on interventions to prevent Alzheimer disease and related dementias (ADRD). These were published in a series in early 2018. Funded by the Agency for Healthcare Research and Quality (AHPQ), EPC systematic reviews provide an evidence base and help inform the USPSTF. In an editorial concerning these reviews, Eric Larson stated, “Although we found some intriguing positive results ... nothing even approached the evidence level required for a USPSTF recommendation.

10. Insufficient evidence for MindGames in preventing dementia

Background: Structured activities to stimulate brain function-that is, cognitive training exercises-are promoted to slow or prevent cognitive decline, including dementia, but their effectiveness is highly debated.
Purpose: To summarize evidence on the effects of cognitive training on cognitive performance and incident dementia outcomes for adults with normal cognition or mild cognitive impairment (MCI).
Data Sources: Ovid MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and PsycINFO through July 2017, supplemented by hand-searches.
Study Selection: Trials (published in English) lasting at least 6 months that compared cognitive training with usual care, waitlist, information, or attention controls in adults without dementia.
Data Extraction: Single-reviewer extraction of study characteristics confirmed by a second reviewer; dual-reviewer risk-of-bias assessment; consensus determination of strength of evidence. Only studies with low or medium risk of bias were analyzed.
Data Synthesis: Of 11 trials with low or medium risk of bias, 6 enrolled healthy adults with normal cognition and 5 enrolled adults with MCI. Trainings for healthy older adults were mostly computer based; those for adults with MCI were mostly held in group sessions. The MCI trials used attention controls more often than trials with healthy populations. For healthy older adults, training improved cognitive performance in the domain trained but not in other domains (moderate-strength evidence). Results for populations with MCI suggested no effect of training on performance (low-strength and insufficient evidence). Evidence for prevention of cognitive decline or dementia was insufficient. Adverse events were not reported.
Limitation: Heterogeneous interventions and outcome measures; outcomes that mostly assessed test performance rather than global function or dementia diagnosis; potential publication bias.
Conclusion: In older adults with normal cognition, training improves cognitive performance in the domain trained. Evidence regarding prevention or delay of cognitive decline or dementia is insufficient.
Primary Funding Source: Agency for Healthcare Research and Quality.
Reference: *Butler M et al. Does Cognitive Training Prevent Cognitive Decline?: A Systematic Review. Ann Intern Med. 2018 Jan 2;168(1):63-68.*

11. No evidence for pharmacological treatments for cognitive protection

Background: Optimal treatment to prevent or delay cognitive decline, mild cognitive impairment (MCI), or dementia is uncertain.
Purpose: To summarize current evidence on the efficacy and harms of pharmacologic interventions to prevent or delay cognitive decline, MCI, or dementia in adults with normal cognition or MCI.
Data Sources: Several electronic databases from January 2009 to July 2017, bibliographies, and expert recommendations.
Study Selection: English-language trials of at least 6 months' duration enrolling adults without dementia and comparing pharmacologic interventions with placebo, usual care, or active control on cognitive outcomes.
Data Extraction: Two reviewers independently rated risk of bias and strength of evidence; 1 extracted data, and a second checked accuracy.
Data Synthesis: Fifty-one unique trials were rated as having low to moderate risk of bias (including 3 that studied dementia medications, 16 antihypertensives, 4 diabetes medications, 2 nonsteroidal anti-inflammatory drugs [NSAIDs] or aspirin, 17 hormones, and 7 lipid-lowering agents). In persons with normal cognition, estrogen and estrogen-progestin increased risk for dementia or a combined outcome of MCI or dementia (1 trial, low strength of evidence); high-dose raloxifene decreased risk for MCI but not for dementia (1 trial, low strength of evidence); and antihypertensives (4 trials), NSAIDs (1 trial), and statins (1 trial) did not alter dementia risk (low to insufficient strength of evidence). In persons with MCI, cholinesterase inhibitors did not reduce dementia risk (1 trial, low strength of evidence). In persons with normal cognition and those with MCI, these pharmacologic treatments neither improved nor slowed decline in cognitive test performance (low to insufficient strength of evidence). Adverse events were inconsistently reported but were increased for estrogen (stroke), estrogen-progestin (stroke, coronary heart disease, invasive breast cancer, and pulmonary embolism), and raloxifene (venous thromboembolism).
Limitation: High attrition, short follow-up, inconsistent cognitive outcomes, and possible selective reporting and publication.
Conclusion: Evidence does not support use of the studied pharmacologic treatments for cognitive protection in persons with normal cognition or MCI.
Primary Funding Source: Agency for Healthcare Research and Quality.
Reference: *Fink HA et al. Pharmacologic Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review. Ann Intern Med. 2018 Jan 2;168(1):39-51.*

12. Insufficient evidence for OTC supplements for cognitive protection

Background: Optimal interventions to prevent or delay cognitive decline, mild cognitive impairment (MCI), or dementia are uncertain.
Purpose: To summarize the evidence on efficacy and harms of over-the-counter (OTC) supplements to prevent or delay cognitive decline, MCI, or clinical Alzheimer-type dementia in adults with normal cognition or MCI but no dementia diagnosis.
Data Sources: Multiple electronic databases from 2009 to July 2017 and bibliographies of systematic reviews.
Study Selection: English-language trials of at least 6 months' duration that enrolled adults without dementia and compared cognitive outcomes with an OTC supplement versus placebo or active controls.
Data Extraction: Extraction performed by a single reviewer and confirmed by a second reviewer; dual-reviewer assessment of risk of bias; consensus determination of strength of evidence.
Data Synthesis: Thirty-eight trials with low to medium risk of bias compared ω-3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C or β-carotene, multi-ingredient supplements, or other OTC interventions with placebo or other supplements. Few studies examined effects on clinical Alzheimer-type dementia or MCI, and those that did suggested no benefit. Daily folic acid plus vitamin B12 was associated with improvements in performance on some objectively measured memory tests that were statistically significant but of questionable clinical significance. Moderate-strength evidence showed that vitamin E had no benefit on cognition. Evidence about effects of ω-3 fatty acids, soy, ginkgo biloba, folic acid alone or with other B vitamins, β-carotene, vitamin C, vitamin D plus calcium, and multivitamins or multi-ingredient supplements was either insufficient or low-strength, suggesting that these supplements did not reduce risk for cognitive decline. Adverse events were rarely reported.
Limitation: Studies had high attrition and short follow-up and used a highly variable set of cognitive outcome measures.
Conclusion: Evidence is insufficient to recommend any OTC supplement for cognitive protection in adults with normal cognition or MCI.
Primary Funding Source: Agency for Healthcare Research and Quality.
***Reference**: Butler M et al. Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review. Ann Intern Med. 2018 Jan 2;168(1):52-62.*

13. PubMed: Physical Activity interventions to prevent cognitive decline or AD is insufficient

Background: The prevalence of cognitive impairment and dementia is expected to increase dramatically as the population ages, creating burdens on families and health care systems.
Purpose: To assess the effectiveness of physical activity interventions in slowing cognitive decline and delaying the onset of cognitive impairment and dementia in adults without diagnosed cognitive impairments.
Data Sources: Several electronic databases from January 2009 to July 2017 and bibliographies of systematic reviews.
Study Selection: Trials published in English that lasted 6 months or longer, enrolled adults without clinically diagnosed cognitive impairments, and compared cognitive and dementia outcomes between physical activity interventions and inactive controls.
Data Extraction: Extraction by 1 reviewer and confirmed by a second; dual-reviewer assessment of risk of bias; consensus determination of strength of evidence.
Data Synthesis: Of 32 eligible trials, 16 with low to moderate risk of bias compared a physical activity intervention with an inactive control. Most trials had 6-month follow-up; a few had 1- or 2-year follow-up. Evidence was insufficient to draw conclusions about the effectiveness of aerobic training, resistance training, or tai chi for improving cognition. Low-strength evidence showed that multicomponent physical activity interventions had no effect on cognitive function. Low-strength evidence showed that a multidomain intervention comprising physical activity, diet, and cognitive training improved several cognitive outcomes. Evidence regarding effects on dementia prevention was insufficient for all physical activity interventions.
Limitation: Heterogeneous interventions and cognitive test measures, small and underpowered studies, and inability to assess the clinical significance of cognitive test outcomes.
Conclusion: Evidence that short-term, single-component physical activity interventions promote cognitive function and prevent cognitive decline or dementia in older adults is largely insufficient. A multidomain intervention showed a delay in cognitive decline (low-strength evidence).
Primary Funding Source: Agency for Healthcare Research and Quality.
***Reference**: Brasure M et al. Physical Activity Interventions in Preventing Cognitive Decline and Alzheimer-Type Dementia: A Systematic Review. Reference: Ann Intern Med. 2018 Jan 2;168(1):30-38.*

As Larson stated “To put it simply, all evidence indicates that there is no magic bullet.”

Advanced Care Planning (ACP)

An easy to use interactive website designed to help older adults engage in advanced care planning through a simple 5-step process and videos has been shown to increase ACP documentation by 10% (www.prepareforyourcare.org)

14. Advanced care planning website associated with ↑ ACP documentation

Importance: Documentation rates of patients' medical wishes are often low. It is unknown whether easy-to-use, patient-facing advance care planning (ACP) interventions can overcome barriers to planning in busy primary care settings.

Objective: To compare the efficacy of an interactive, patient-centered ACP website (PREPARE) with an easy-to-read advance directive (AD) to increase planning documentation.
Design, Setting, and Participants: This was a comparative effectiveness randomized clinical trial from April 2013 to July 2016 conducted at multiple primary care clinics at the San Francisco VA Medical Center. Inclusion criteria
were age of a least 60 years; at least 2 chronic and/or serious conditions; and 2 or more primary care visits; and 2 or more additional clinic, hospital, or emergency room visits in the last year.
Interventions: Participants were randomized to review PREPARE plus an easy-to-read AD or the AD alone. There were no clinician and/or system-level interventions or education. Research staff were blinded for all follow-up
measurements.
Main Outcomes and Measures: The primary outcome was new ACP documentation (ie, legal forms and/or discussions) at 9 months. Secondary outcomes included patient-reported ACP engagement at 1 week, 3 months, and 6 months using validated surveys of behavior change process measures (ie, 5-point knowledge,self-efficacy, readiness scales) and action measures (eg, surrogate designation, using a 0-25 scale). We used intention-to-treat, mixed-effects logistic and linear regression, controlling for time, health literacy, race/ethnicity, baseline ACP, and clustering by physician.
Results: The mean (SD) age of 414 participants was 71 (8) years, 38 (9%) were women, 83 (20%) had limited literacy, and 179 (43%) were nonwhite. No participant characteristic differed significantly among study arms at baseline. Retention at 6 months was 90%. Advance care planning documentation 6 months after enrollment was higher in the PREPARE arm vs the AD-alone arm (adjusted 35% vs 25%; odds ratio, 1.61 [95% CI, 1.03-2.51]; P = .04). PREPARE also resulted in higher self-reported ACP engagement at each follow-up, including higher process and action scores; P <.001 at each follow-up).
Conclusions and Relevance: Easy-to-use, patient-facing ACP tools, without clinician- and/or system-level interventions, can increase planning documentation 25% to 35%. Combining the PREPARE website with an easy-to-read AD resulted in higher planning documentation than the AD alone, suggesting that PREPARE may increase planning documentation with minimal health care system resources.
Trial Registration: clinicaltrials.gov Identifier: NCT01550731.
Reference: *Sudore RL et al. Effect of the PREPARE Website vs an Easy-to-Read Advance Directive on Advance Care Planning Documentation and Engagement Among Veterans: A Randomized Clinical Trial.JAMA Intern Med. 2017 Aug 1;177(8):1102-1109.*

Miscellaneous

15. Melatonin helpful for sleep disorders in dementia

BACKGROUND: Sleep disturbance may affect up to half of elderly patients with dementia and is a possible contributor to cognitive impairment. Melatonin replacement may improve both sleep and cognition.
METHODS: These authors, from China and the USA, performed a literature review and meta-analysis to determine whether melatonin has therapeutic benefit for patients with dementia. The investigators identified seven randomized controlled trials that included 520 patients with dementia treated with melatonin versus placebo or light therapy. Primary outcomes were the effects of melatonin on sleep disturbance and on cognitive function as assessed by the Mini-Mental State Examination (MMSE).
RESULTS: Melatonin given for more than four weeks (but not shorter durations) improved sleep efficacy (four trials; p=0.02), and four weeks of melatonin also lengthened total sleep time by 28 minutes (six trials; p=0.02). Results on the MMSE (five trials) did not change significantly after melatonin treatment and there was, likewise, no significant effect of melatonin on cognitive function as assessed using the Alzheimer's Disease Assessment-Cognitive subscale (two trials). For subgroups with Alzheimer's disease, melatonin significantly improved sleep efficacy but had no effect on total sleep time or cognition. Adverse events, when reported, did not differ significantly between the melatonin and placebo groups. Study limitations included the wide range of sleep measures and melatonin doses.
CONCLUSIONS: Melatonin may help improve sleep in patients with dementia but appears to have no impact on cognitive function. 34 references.
REFERENCE: *Xu, J., et al MELATONIN FOR SLEEP DISORDERS AND COGNITION IN DEMENTIA: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS. Am J Alzheimers Dis Other Demen 30(5):439, August 2015*

There exist in no randomize trials comparing the difference in mortality quality-of-life in dementia patients who have been provided PEG feeding versus regular oral feedings; **all studies have been observational**. A 2009 Cochran review demonstrated there was no evidence for increased survival in dementia patients who received enteral tube feedings. Abstract # 16 was a retrospective analysis from a prospect of database of 392 patient who underwent PEG placement between 2008 and 2013 The patient's were classified into 3 categories 1) dementia, 2) CVA, and 3) other indications (including oropharyngeal cancer and motor neuron disease). Outcome data included biochemical markers of nutritional status, rehospitalization rates and survival rates, measured 18 months after PEG insertion The group with dementia (n = 165; mean age 83) was compared to the group with a CVA (n=124; mean age 79) and a group with other PEG indications (n=103; mean age 77). Clinical reasons for PEG placement included: refusing to eat, dysphasia, recurrent aspiration, altered mental status, and others.

- Rehospitalization rates 6 months post procedure were 2.45 vs 1.86 vs 1.65

- Mortality within the first year post PEG placement was 75% vs 58% vs 38%
- 1 month mortality post procedure was 15% vs 3.3% vs 7.8%
- The presence of dementia was associated the mean time to death 7.2 vs 8.9 vs 8 months
- Additionally, a 2.3 gram/dL decrease in albumin was noted in the dementia group whereas the other 2 groups a slightly smaller decreases in albumin

Thus, there was no increased survival, rehospitalization or improved albumin patients with dementia receiving a PEG vs those with a PEG for other reasons

16. PEG Placement has no effect on dementia outcomes

BACKGROUND: Percutaneous endoscopic gastrostomy (PEG) tubes are commonly utilized as a method of enteral feeding in patients unable to obtain adequate oral nutrition. Although some studies have shown improved mortality in select populations, the safety and effectiveness of PEG insertion in patients with dementia compared with those with other neurological diseases or head and neck malignancy remains less well defined.
OBJECTIVE: To evaluate the nutritional effectiveness, rate of rehospitalization, and risk of mortality among patients with dementia compared with patients with other neurological diseases or head and neck cancers who undergo PEG placement.
MATERIALS AND METHODS: We conducted a retrospective analysis from a prospective database of patients who underwent PEG placement at an academic tertiary center between 2008 and 2013. The following data were collected: indication for PEG, patient demographics, biochemical markers of nutritional status rehospitalization, and survival rates.
RESULTS: During the study period, 392 patients underwent PEG tube placement. Indications for PEG were dementia (N=165, group A), cerebrovascular accident (N=124, group B), and other indications such as oropharyngeal cancers and motor neuron disease (N=103, group C). The mean follow-up time after PEG was 18 months (range, 3 to 36 mo). No differences in baseline demographics were noted. PEG insertion in the dementia (group A) neither reduced the rehospitalization rate 6 months' postprocedure compared with groups B and C (2.45 vs. 1.86 and 1.65, respectively; P=0.05), nor reduced the mortality rate within the first year post-PEG placement (75% vs. 58% and 38% for groups A, B, and C, respectively=0.001), as well, it did not improve survival at 1 month after the procedure (15% vs. 3.26% and 7.76%, for groups A, B, C, respectively, P<0.01). The presence of dementia was also associated with shorter mean time to death (7.2 vs. 8.85 and 8 mo for groups A, B, C, respectively, P<0.05). The rate of improvement of the nutritional biomarker albumin was lower in the dementia group [3.1. to 2.9 vs. 3.2 to 3.3 and 3 to 3.3 g/dL for groups A, B, and C, respectively (P<0.02)]. Multivariate regression analysis showed that the presence of dementia was an independent predictor for mortality rate within the first year and 1-month mortality rate in patients undergoing PEG insertion with odds ratio 3.22 (95% confidence interval, 1.52-4.32) and odds ratio 2.52 (95% confidence interval, 1.22-3.67).
CONCLUSIONS: PEG insertion in patients with dementia neither improve both short-term and long-term mortality nor rehospitalization rate as compared with patients who underwent PEG placement for alternate indications such as other neurological diseases or head and neck malignancy and even was associated with shorter time to death. Furthermore, PEG insertion in patients with dementia did not improve albumin. Therefore, careful selection of patients with dementia is warranted before PEG placement weighing the risks and benefits on a personalized basis.
REFERENCE: REFERENCE*: Ayman, A.R., et al. PEG INSERTION IN PATIENTS WITH DEMENTIA DOES NOT IMPROVE NUTRITIONAL STATUS AND HAS WORSE OUTCOMES AS COMPARED WITH PEG INSERTION FOR OTHER INDICATIONS. J Clin Gastroenterol 51(5):417, May/June 2017*

Bottom Lines

1. Mild cognitive impairment (MCI) appears reversible
2. Cumulative anticholinergic use is associated with an increased risk for dementia
3. No association exists between proton pump inhibitor use and risk of Alzheimer's Disease
4. Many brain disorders manifest later in life but, in fact, are life-course illnesses and there is a vascular component in up to 80%.
5. About 35% of the risk of dementia is potentially modifiable with lifestyle modification
6. Certain interventions (including resource intensive multidomain interventions) and the Mediterranean diet are associated with improved cognitive function
7. There is no evidence that single interventions (such as cognitive training, pharmacological treatments, OT supplements and exercise) are not associated with improved cognitive outcomes
8. Advanced care planning is facilitated with an easy to use online resource
9. PEG placement has no effect on dementia outcomes

Appendix

Note that The Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 has stopped using the word dementia (phrase associated with stigma) and instead uses the phrase “major neurocognitive disorders”.

10 ways to love your brain (from the Alzheimer’s Association)

1. Break a sweat.
    a. Engage in regular cardiovascular exercise that elevates your heart rate and increases blood flow to the brain and body. Several studies have found an association between physical activity and reduced risk of cognitive decline.
2. Hit the books.
    a. Formal education in any stage of life will help reduce your risk of cognitive decline and dementia. For example, take a class at a local college, community center or online.
3. Butt out.
    a. Evidence shows that smoking increases risk of cognitive decline. Quitting smoking can reduce that risk to levels comparable to those who have not smoked.
4. Follow your heart.
    a. Evidence shows that risk factors for cardiovascular disease and stroke — obesity, high blood pressure and diabetes — negatively impact your cognitive health. Take care of your heart, and your brain just might follow.
5. Heads up!
    a. Brain injury can raise your risk of cognitive decline and dementia. Wear a seat belt, use a helmet when playing contact sports or riding a bike, and take steps to prevent falls.
6. Fuel up right.
    a. Eat a healthy and balanced diet that is lower in fat and higher in vegetables and fruit to help reduce the risk of cognitive decline. Although research on diet and cognitive function is limited, certain diets, including Mediterranean and Mediterranean-DASH (Dietary Approaches to Stop Hypertension), may contribute to risk reduction.
7. Catch some zzz's.
    a. Not getting enough sleep due to conditions like insomnia or sleep apnea may result in problems with memory and thinking.
8. Take care of your mental health.
    a. Some studies link a history of depression with increased risk of cognitive decline, so seek medical treatment if you have symptoms of depression, anxiety or other mental health concerns. Also, try to manage stress.
9. Buddy up.
    a. Staying socially engaged may support brain health. Pursue social activities that are meaningful to you. Find ways to be part of your local community — if you love animals, consider volunteering at a local shelter. If you enjoy singing, join a local choir or help at an afterschool program. Or, just share activities with friends and family.
10. Stump yourself.
    a. Challenge and activate your mind. Build a piece of furniture. Complete a jigsaw puzzle. Do something artistic. Play games, such as bridge, that make you think strategically. Challenging your mind may have short and long-term benefits for your brain.

Life-course model of contribution of modifiable risk factors to dementia (from the Lancet Commission Article)

1. Aspirin alone may be sufficient protection from postop VTE after total knee arthroplasty

Clinical question: Is aspirin alone effective in preventing postoperative venous thromboembolism in adults after total knee arthroplasty?
Study design: Cohort (retrospective) **Funding source:** Self-funded or unfunded
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: These investigators analyzed data from a retrospective cohort of 49,221 consecutive unilateral TKAs performed at a coalition of Michigan hospitals between April 2013 and October 2015. The exposure variable was treatment for VTE prophylaxis during the 3-day perioperative window, including aspirin alone, aspirin plus additional non-aspirin anticoagulation (eg, warfarin, direct-factor Xa inhibitors, low-molecular-weight heparin), non-aspirin anticoagulation only, or no pharmaco-prophylaxis. The primary outcome was a composite of pulmonary embolism, deep venous thrombosis, or death during the 90-day postoperative period. The secondary outcome was the occurrence of a major bleeding event. Patients who received no prophylaxis had a significantly increased risk of a VTE event compared with those who received prophylaxis, but there were no significant differences in the rates of a VTE event in patients who took aspirin alone compared with other prophylactic regimens. Similarly, no significant differences in major bleeding events occurred in the aspirin-only versus other prophylactic regimens groups. During the study period the use of aspirin alone as the agent of choice for prophylaxis following TKA rose from 10.2% to 50.0% with no concurrent rise in the rate of VTE events or bleeding events.
Bottom line: This study found no significant differences in the risk of a venous thromboembolic (VTE) event or a major bleeding episode in adults given aspirin alone compared with other anticoagulation agents for prophylaxis following a total knee arthroplasty (TKA). This retrospective study may be biased because lower-risk patients were more likely to be given aspirin only. However, a recent randomized trial also reported similar efficacy for low-dose aspirin compared with rivaroxaban for the prevention of symptomatic VTE or major bleeding episodes following TKA. (LOE = 2b-)
Hood BR, Cowen ME, Zheng HT, Hughes RE, Singal B, Hallstrom BR. Association of aspirin with prevention of venous thromboembolism in patients after total knee arthroplasty compared with other anticoagulants. A noninferiority analysis. 2018 Oct 17. doi: 10.1001/jamasurg.2018.3858. [Epub ahead of print]

2. Deprescribing is safe, but at the risk of symptom recurrence

Clinical question: Is deprescribing long-term medication safe and effective?
Study design: Systematic review **Funding source:** Self-funded or unfunded
Setting: Outpatient (any)
Synopsis: These authors searched PubMed and EMBASE for randomized trials that compared deprescribing (ie, the process of withdrawing unnecessary medications) with placebo or usual care. Two authors independently assessed the inclusion of studies and the risk of bias for each study. Although they reviewed the reference lists of the included studies, the authors don't describe a formal search or formal assessment of the potential of publication bias. Ultimately, they included 27 studies, each of which included between 20 and 2471 patients. Sixteen of the studies used placebo and 11 used usual care as the comparator. The studies evaluated a wide range of drug classes, including antihypertensives, antipsychotics, corticosteroids, and so forth. The authors quite reasonably decided against pooling data because of the marked variability in the target drugs, target group (eg, mean age varied between 50 and 89 years of age), and follow-up duration (4 weeks to 5 years). Only 10 of the studies were of low risk of bias. The rate of successful deprescribing varied from 20% to 100%; in 19 of the studies the rate of successful deprescribing exceeded 50%. Sixteen of the studies reported on symptom relapse or resumption of deprescribed medications (range 0% to 80%). Among the nine placebo-controlled studies reporting on relapse, 5 found significantly greater relapse in the intervention groups (rate difference ranged from 14% to 50%). The included studies found that adverse events were infrequent.
Bottom line: The limited rigorous data on deprescribing suggest that many patients can safely stop unnecessary medication but symptom relapse is significant. (LOE = 1a-)
Thio SL, Nam J, van Driel ML, Dirven T, Blom JW. Effects of discontinuation of chronic medication in primary care: a systematic review of deprescribing trials. Br J Gen Pract 2018;68(675):e663-e672.

3. Aspirin's benefits and harms are less clear for primary prevention in moderate-risk patients (ARRIVE)

Clinical question: Is low-dose aspirin effective for the primary prevention of cardiovascular disease in moderate-risk patients?
Study design: Randomized controlled trial (double-blinded) **Funding source:** Industry
Allocation: Concealed
Setting: Outpatient (any)
Synopsis: Low-dose aspirin for secondary prevention and in the face of acute coronary events is pretty much a slam dunk. But despite of years of research, several meta-analyses, and numerous guidelines, its use for primary prevention still seems to rile people up. These researchers point out that most of the recommendations are largely for patients whose 10-year risk of a coronary event exceeds 20% and the role of aspirin in patients of intermediate risk is less clear. So, they conducted a double-blind randomized trial of 100 mg aspirin daily (n = 6270) or placebo (n = 6276) in patients at moderate risk of coronary artery disease. The study participants were men at least 55 years of age or women at least 60 years of age with a 10% to 20% 10-year risk based on age, sex, smoking status, blood pressure, lipid concentrations, and family history. They excluded patients with diabetes and those at high risk for bleeding complications. Using intention-to-treat analysis, after 5 years the rate of events (a composite of myocardial infarction, stroke,

cardiovascular death, unstable angina, or transient ischemic attack) was similar between the treatment groups (4.3% vs 4.5%, respectively). The overall death rate was the same (2.6%) in each group. The aspirin-treated patients had more bleeding events (1% vs 0.5%), although very few had moderate or severe gastrointestinal bleeding. The graphs in the paper demonstrate nearly a linear relationship in outcomes over time, so the projected 10-year outcomes indicate that 9% of the placebo-treated patients would have had a coronary event. Recall last month another study that suggested aspirin's effect was potentially influenced by weight and sex (Rothwell et al. Lancet 2018;392(10145):387-399).
Bottom line: In this study, after 5 years of treatment, patients at moderate risk of heart disease who took low-dose aspirin did not show a decrease in coronary events and all-cause mortality, and had slightly more, albeit minor, gastrointestinal bleeding. If you are confused by all the aspirin-related folderol of late, join the club. Using aspirin for primary prevention of cardiovascular disease is not a one-size-fits-all proposition. We need to risk-stratify patients according to benefits and harms and engage in shared decision-making with each patient. (LOE = 1b)
Gaziano JM, Brotons C, Coppolecchia R, et al, for the ARRIVE Executive Committee. 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. Lancet 2018;392(10152):1036-1046.

4. USPSTF 2018 recommends intimate partner violence screening in women of reproductive age (B recommendation)

Clinical question: Should primary care clinicians screen adult women for intimate partner violence and/or screen older or vulnerable adults for abuse?
Study design: Practice guideline **Funding source:** Government
Setting: Population-based
Synopsis: In this updated 2018 version, the task force analyzed 3 randomized controlled trials (RCTs) that compared IPV screening with no screening and found no direct improvement in patient-oriented outcomes when screening was followed only by brief counseling or referral. Two of these RCTs reported on harms of screening and found none. Nine studies assessed screening tools, with sensitivities ranging from 64% to 87% and specificities ranging from 80% to 95%. Eleven RCTs evaluated interventions for women with screen-detected IPV or at high risk for IPV, and the most effective trials for IPV outcomes involved ongoing support services. Such services included multiple visits, with behavioral and social interventions addressing other pregnancy-related risk factors in addition to IPV, including smoking, depression, and tobacco exposure. Of the 3 RCTs that enrolled pregnant women and evaluated a counseling intervention, 2 found benefit. No studies evaluated screening or interventions for elder abuse and neglect. The American Academy of Family Physicians, American College of Obstetricians and Gynecologists, and American Academy of Pediatrics recommend screening for IPV. The Canadian Task Force on Preventive Health Care and the World Health Organization do not recommend screening for IPV on the basis of insufficient evidence of direct benefit.
Bottom line: In this updated 2018 review, the U.S. Preventive Services Task Force (USPSTF) concludes there is sufficient evidence to recommend screening for intimate partner violence (IPV) in women of reproductive age where ongoing support services are available (B recommendation). The USPSTF concludes that there is insufficient evidence to recommend screening for abuse and neglect in older or vulnerable adults (I statement). These recommendations are unchanged from the 2013 USPSTF recommendations. (LOE = 2c)
US Preventive Services Task Force. Screening for intimate partner violence, elder abuse, and abuse of vulnerable adults. US Preventive Services Task Force recommendation statement. JAMA 2018;320(16):1678-1687.

5. 60% of adults treated with abx for acute appendicitis do not require appendectomy at 5 years

Clinical question: What is the likelihood of a late recurrence of appendicitis in adults initially given antibiotic therapy for uncomplicated acute appendicitis?
Study design: Randomized controlled trial (single-blinded) **Funding source:** Government
Allocation: Concealed
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: These investigators are publishing 5-year follow-up data from a study that compared immediate surgery to antibiotic therapy in 530 adults aged 18 years to 60 years (Salminen P, et al. JAMA 2015;313(23):2340-48). The original trial reported after 1 year approximately 75% of adults treated initially with antibiotics did not require appendectomy. After the first-year follow-up, the investigators conducted telephone interviews 3 to 5 years after the intervention and performed a search of hospital records for those patients who could not be reached. Using intention-to-treat analysis, the cumulative incidence of acute appendicitis recurrence in the antibiotic group was 39.5% (95% CI 33.1% - 45.3%) at 5 years. Of the 85 patients in the antibiotic group who underwent appendectomy for presumed recurrence, no appendicitis was found in 7 patients, resulting in a true recurrence rate of 32.4%. The overall complication rate was similar between surgically treated patients who were initially randomized to the antibiotic group and those randomized to the immediate appendectomy group. The overall complication rate was significantly lower, however, in the subgroup of patients who underwent laparoscopic appendectomy (7.5%) than in the open appendectomy group. Thus, the potential benefits of antibiotics versus immediate surgery may be reduced with the laparoscopic approach.
Bottom line: This study found that more than 60% of adults who presented with uncomplicated appendicitis were successfully treated with antibiotics alone. Those patients who developed recurrent disease and required surgical intervention within 5 years did not experience any additional adverse outcomes related to the delay. Of the 257 patients initially randomized to receive antibiotic therapy, 70 underwent appendectomy within the first year, with 30 additional patients undergoing appendectomy between years 1 and 5.
Salminen P, Tuominen R, Paajanen H, et al. Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. JAMA 2018;320(12):1259-1265.

6. Gabapentin and pregabalin not effective for low back pain with or without radiculopathy

Clinical question: Are anticonvulsants an effective treatment for low back pain?
Study design: Meta-analysis (randomized controlled trials) **Funding source:** Self-funded or unfunded
Setting: Various (meta-analysis)
Synopsis: Particularly in this era of heightened awareness of the potential harms of opioids, anticonvulsants are often prescribed for the treatment of painful conditions. Although there is evidence of their effectiveness primarily for peripheral and diabetic neuropathy, they are increasingly prescribed for other conditions, including low back pain. This systematic review included a comprehensive search of the literature and the authors identified 9 randomized trials (3 of which were crossover studies) that compared topiramate, pregabalin, or gabapentin with placebo in patients with low back pain with or without radiculopathy. They excluded studies of pregnant women; pre-operative patients; and patients with mixed conditions, such as neck and back pain. The trials were assessed for risk of bias, and only 1 was at high risk. The studies used a range of pain scales, so the standardized mean difference in pain scores between treatment and placebo groups was the primary outcome. The 9 studies reported a total of 14 comparisons, with only 2 showing a statistically significant benefit. One was a small study of high-dose gabapentin (3600 mg/day) in 43 patients with lumbar radicular pain, and the other was a study of 96 patients with low back pain who were given 300 mg topiramate 300 each day. The other topiramate study found no benefit, as did none of the other studies of pregabalin or gabapentin. Where results could be pooled, there was essentially no difference between groups. Where results could be pooled, there was essentially no difference between groups. There was no difference in serious adverse events: 4 in the pregabalin group, 6 in the placebo group (though these were reported in only 2 studies with a total of 423 patients). Any adverse events, however, were significantly more common with active treatment (relative risk 1.4; 95% CI 1.2 - 1.7).
Bottom line: The use of anticonvulsants like gabapentin for painful conditions has increased greatly in recent years. This review finds good evidence that these drugs are not an effective treatment for low back pain with or without radiculopathy, and are associated with an increased risk for adverse events. (LOE = 1a)
Enke O, New HA, New CH, et al. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. CMAJ 2018;190(26):E786-E793.

7. A single blood pressure measurement is often falsely elevated

Clinical question: Is a single office blood pressure measurement reliable to assess hypertension?
Study design: Cross-sectional **Funding source:** Self-funded or unfunded
Setting: Outpatient (primary care)
Synopsis: The authors enrolled 1000 consecutive patients who presented for internal medicine, obstetric, or gynecologic care, though only 802 patients completed the study. Each patient, after 5 minutes of rest, had 4 consecutive blood pressure measurements, 2 minutes apart, by 1 of 13 trained physicians. The first systolic blood pressure was more than 10 mm Hg higher than the mean of subsequent measurements in 23.9% of patients; in total, 45.9% of patients had a systolic difference of more than 5 mm Hg. Similarly, diastolic blood pressures were more than 10 mm Hg different in 4.4% of patients; in total, 21.6% of patients had a difference of more than 5 mm Hg. More important, hypertension would have been diagnosed in error in 1 in 8 patients (12%) if only the first measurement had been obtained, and 2% of patients would have had their hypertension undiagnosed by the single measurement.
Bottom line: Don't rely on a single blood pressure measurement. The first blood pressure reading taken during an office visit will be substantially different than subsequent readings in almost half of typical patients, and if relied upon will result in 1 in 8 patients being falsely labeled as hypertensive. (LOE = 1b)
Burkhard T, Mayr M, Winterhalder C, Leonardi L, Eckstein J, Vischer AS. Reliability of single office blood pressure measurements. Heart 2018;104(14):1173-1179.

8. Incidental findings are common with chest CT and MRI of the spine and brain

Clinical question: What is the likelihood and outcomes of incidental findings on imaging tests?
Study design: Systematic review **Funding source:** Self-funded or unfunded
Setting: Various (meta-analysis)
Synopsis: These authors searched 2 databases and reference lists of included papers to identify 20 systematic reviews of observational studies that gave a prevalence of incidental abnormalities ("incidentalomas") in patients already being imaged for cancer. Incidentalomas were defined differently across the systematic reviews. CT of the chest resulted in incidentalomas reported in 45% of patients (95% CI 36% - 55%). The relatively new CT colonoscopy resulted in incidental findings in 38% of patients (21% - 57%). Magnetic resonance imaging also reported incidental findings when imaging the spine (22%) and brain (22%). Whole body positron emission tomography (PET) and PET/computed tomography had rates of 2% (95% CI 1% to 4%). No studies have determined the prevalence of incidentalomas identified via radiography or ultrasound. Malignancy of incidentalomas were highest with breast findings (42%; 31% - 54%). Renal, thyroid, and ovarian findings were malignant approximately 25% of the time. Extra-colonic, prostatic, and colonic incidentalomas were malignant 10% to 20% of the time. Rates of incidentalomas varied substantially among the meta-analyses.
Bottom line: The risks of imaging, in addition to radiation exposure, also include the identification of "Incidentalomas," which can lead to patient anxiety, further testing, and overtreatment, and there is little research to guide what to do when they pop up on an imaging report (as the famous dodge "clinical correlation needed"). Computerized tomography (CT) of the chest (45%), CT colonoscopy (38%), and cardia magnetic resonance imaging (34%) commonly produce incidental findings. The rate of malignancy in incidentalomas was high in breast (42%) and ovary (28%) fidnings; intermediate in prostatic and colonic (10% - 20%) findings; and low in brain, parotid, and adrenal gland (< 5%) findings. Although everyone has a story of the lifesaving results of such serendipity, we don't often consider the patients subjected to unneeded testing and treatment, the so-called Victims Of Modern Imaging Technology—you can figure out the acronym (BMJ 2003;326:1273). (LOE = 2a)

O'Sullivan JW, Muntinga T, Grigg S, Ioannidis JP. Prevalence and outcomes of incidental imaging findings: umbrella review. BMJ 2018;361:k2387.

9. Lower systolic BP during antihypertensive treatment associated with more deaths in the elderly

Clinical question: Is lower systolic blood pressure associated with better outcomes in elderly patients who take antihypertension medications?
Study design: Cohort (prospective) **Funding source:** Government
Setting: Population-based
Synopsis: Are you tired of all the ping-ponging, guideline-based blood pressure targets? Unfortunately, this study won't improve your fatigue. These researchers assembled a cohort of 570 residents of Leiden in the Netherlands who turned 85 years of age between 1997 and 1999. They excluded people who died within 3 months of enrollment and those who had no blood pressure measurement at baseline. At baseline, and periodically over the course of 5 years of follow up, the researchers collected all kinds of information: sociodemographics, medical diagnoses, medications, mental status, grip strength (as a proxy for frailty), blood pressure, and so forth. They assessed the main outcome—death from any cause—by using municipal records. Slightly fewer than half of the residents (44%) took antihypertensive medications at baseline; these patients were more likely to have other cardiovascular disorders than those not taking antihypertensive medications (62% vs 36%). During the 5 years of follow-up, 263 (46%) participants died. For those taking antihypertensive medications, all-cause mortality was significantly higher with decreasing systolic blood pressure (hazard ratio 1.29 per 10 mmHg lower systolic blood pressure; 95% CI 1.15 - 1.46). For the residents who were not taking antihypertensive medications, there was no significant correlation between systolic blood pressure and all-cause mortality. Additionally, the patients taking antihypertensives had more rapid cognitive decline with lower systolic blood pressure. Although many explanations for the differences in treatment thresholds are given by the various guidelines, one is how we value clinical trial versus observational data: The guidelines that promulgate lower blood pressure targets are more likely to value observational data. The data from this study are subject to many of the biases inherent in cohort studies, but they should moderate the enthusiasm for lower blood pressure targets.
Bottom line: In this small cohort study of patients older than 85 years, lower systolic blood pressure during treatment with antihypertensive medications is associated with higher death rates and greater cognitive decline. (LOE = 1b-)
Streit S, Poortvliet RKE, Gussekloo J. Lower blood pressure during antihypertensive treatment is associated with higher all-cause mortality and accelerated cognitive decline in the oldest-old data from the Leiden 85-plus Study. Age Ageing 2018;47(4):545-550.

10. NPH insulin: fewer episodes of severe hypoglycemia than analogs (Lantus and Levemir) and less than half the cost

Clinical question: Do long-acting insulin analogs, such as glargine (Lantus) or detemir (Levemir), reduce the risk of clinically significant hypoglycemia compared with NPH insulin?
Study design: Cohort (retrospective) **Funding source:** Government
Setting: Population-based
Synopsis: Marketing efforts have convinced most clinicians that long-acting insulin analogs, such as glargine and detemir, reduce the risk of hypoglycemia and are thus safer than traditional NPH insulin. These investigators analyzed data from 2006 and 2015 from multiple patient and prescription registries with the Kaiser Permanente of Northern California. Outcomes of interest included pharmacy use; laboratory results; and outpatient, emergency department, and hospitalization diagnoses of diabetes and related complications. The inception cohort consisted of 25,489 adults, 19 years or older, with type 2 diabetes who were initiating basal insulin therapy without any insulin prescription fills during the prior 12 months. Results were analyzed after controlling for multiple potential confounders, including demographics, index year, clinician specialty, comorbidity index, chronic kidney and/or liver disease, visual impairment, history of depression, glycemic control, history of severe hypoglycemia episodes requiring third-party intervention, and medication nonadherence. The risk of a subsequent severe hypoglycemic episode resulting in an emergency department visit or hospital admission was non-significantly lower in patients who initiated NPH insulin at baseline compared with those initiating insulin analogs (8.8 vs 11.9 events per 1000 person-years, respectively). In addition, glycemic control was significantly more improved in patients using NPH insulin versus insulin analogs (difference in HbA1C -0.22%; 95% CI -0.09% to -0.37%).
Bottom line: This study found that, compared with expensive long-acting insulin analogs costing 2 to 10 times as much, human neutral protamine Hagedorn (NPH) insulin results in a similar number, if not fewer, episodes of severe hypoglycemia that result in emergency department visits and hospitalizations. NPH insulin also improves glycemic control as well, if not better, than insulin analogs. In a previous report (Singh SR, et al. CMAJ 2009;180(4):385-96), overall quality of life was also similar with NPH insulin or insulin analogs. Compared with long-acting insulin analogs, NPH insulin is as Safe if not safer, equally Tolerated, equally or more Effective, and at a much lower Price (STEP). One in 4 adults with diabetes either stop or cut back significantly on their insulin because they can't afford it. (LOE = 2b-)
Lipska KJ, Parker MM, Moffet HH, Huang ES, Karter AJ. Association of initiation of basal insulin analogs vs neutral protamine Hagedorn insulin with hypoglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. JAMA 2018;320(1):53-62.

11. Second blood pressure reading drops 8 mm Hg from initial high reading

Clinical question: In patients with high blood pressure, does a second reading show lower results?
Study design: Cohort (prospective) **Funding source:** Government
Setting: Outpatient (primary care)
Synopsis: This study was conducted in primary care offices of a large US health system. The electronic health record was set to remind clinicians to recheck the blood pressure of a patient when a value greater than 140/90 mm Hg was documented. The reminder

worked: Clinicians rechecked high blood pressures 83% of the time. The authors then evaluated the effect of this simple intervention on 38,260 patients, average age 61 years, 39% of whom had a high initial reading. With repeated measurement, the median drop in blood pressure was 8 mm Hg (interquartile range 2 mm Hg - 17 mm Hg) and 36% of patients no longer had a blood pressure of 140/90 mm Hg or higher.
Bottom line: If you're not rechecking high blood pressures, you should. In fact, set your electronic health record to remind you to do it. In this large study, when reminded, clinicians rechecked elevated blood pressures 83% of the time, finding a median drop in blood pressure of 8 mm Hg during the same visit. That drop is equivalent to a typical reduction in blood pressure with pharmacologic treatment over time and resulted in one-third fewer patients being labeled with high blood pressure at that visit. (LOE = 2b)
Einstadter D, Bolen SD, Misak JE, Bar-Shain DS, Cebul RD. Association of repeated measurements with blood pressure control in primary care. JAMA Intern Med 2018 doi:10.1001/jamainternmed.2018.0315. [Epub ahead of print]

12. Risk of cancer is low in patients with Barrett's esophagus

Clinical question: What is the annual incidence of esophageal cancer among patients with Barrett's esophagus?
Study design: Cohort (prospective) **Funding source:** Government
Setting: Population-based
Synopsis: Previous studies have reported a range of annual incidences of cancer in patients with BE from 0.2% to 0.5%, depending on the location of the study and whether both prevalent and incidence cancers were counted. This is the largest US cohort study; Kaiser Permanente enrolled 8929 patients with BE between 1995 and 2012. The mean age at study entry was 61 years, 66% were men, and mean follow-up was 5.6 years. Cancer incidence and mortality were compared with the entire Kaiser Permanente population, stratified by age and sex. The standardized incidence ratio (SIR) for esophageal cancer (16) and gastric cancer (4.4) was significantly increased in patients with BE. These SIRs were larger in women than in men, although the absolute number of cancers was greater in men. In absolute terms, there was an excess of 44 digestive cancers, slightly more than half of which were esophageal, per 10,000 patient-years of follow-up. The SIRs were greatest in the first 3 years, because of detection of prevalent cancers, and declined to approximately half after 3 years. The incidence of esophageal cancer alone was 24 per 10,000 person-years, or approximately 0.24% per year, which is consistent with the large, well-done Danish registry trial that found a rate of 0.12% after prevalent cancers were excluded (http://www.essentialevidenceplus.com/content/poem/131201).
Bottom line: In patients with Barrett's esophagus (BE), only about 1 in 420 receives a diagnosis of esophageal cancer per year.
Cook MB, Coburn SB, Lam JR, Taylor PR, Schneider JL, Corley DA. Cancer incidence and mortality risks in a large US Barrett's oesophagus cohort. Gut 2018;67(3):418-529.

13. Eating ultra-processed foods increases cancer risk

OBJECTIVE: To assess the prospective associations between consumption of ultra-processed food and risk of cancer.
DESIGN: Population based cohort study.
SETTING AND PARTICIPANTS: 104 980 participants aged at least 18 years (median age 42.8 years) from the French NutriNet-Santé cohort (2009-17). Dietary intakes were collected using repeated 24 hour dietary records, designed to register participants' usual consumption for 3300 different food items. These were categorised according to their degree of processing by the NOVA classification.
MAIN OUTCOME MEASURES: Associations between ultra-processed food intake and risk of overall, breast, prostate, and colorectal cancer assessed by multivariable Cox proportional hazard models adjusted for known risk factors.
RESULTS: Ultra-processed food intake was associated with higher overall cancer risk (n=2228 cases; hazard ratio for a 10% increment in the proportion of ultra-processed food in the diet 1.12 (95% confidence interval 1.06 to 1.18); P for trend<0.001) and breast cancer risk (n=739 cases; hazard ratio 1.11 (1.02 to 1.22); P for trend=0.02). These results remained statistically significant after adjustment for several markers of the nutritional quality of the diet (lipid,sodium, and carbohydrate intakes and/or a Western pattern derived by principal component analysis).
CONCLUSIONS: In this large prospective study, a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer. Further studies are needed to better understand the relative effect of the various dimensions of processing (nutritional composition, food additives, contact materials, and neoformed contaminants) in these associations.
Fiolet T et al. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. BMJ. 2018 Feb 14;360:k322.

14. Intensive primary care weight-loss program results in remission for half of patients with T2DM

Clinical question: Can an intensive weight-management program in primary care settings result in remission of type 2 diabetes?
Study design: Randomized controlled trial (nonblinded) **Funding source:** Government
Allocation: Uncertain
Setting: Outpatient (primary care)
Synopsis: These authors from the Diabetes Remission Clinical Trial (DiRECT) randomized (concealed allocation) 49 primary care practices in Scotland and in the Tyneside region of England to provide a commercial weight-management program (Counterweight Plus) or a control intervention. From within these practices the researchers recruited 306 adults with type 2 diabetes (duration less than 6 years) who had a body mass index between 27 and 45 and were not using insulin. There was no random sampling of patients within each practice. The weight-management program consisted of training the office nurse or dietitian in Counterweight Plus—dietary replacement for 3 months to 5 months using a low-energy formula, followed by 2 weeks to 8 weeks of food re-introduction. The patients in this program stopped taking all oral diabetes drugs and antihypertensive drugs at the beginning of the study. The goal of the

intervention was to induce at least 15 kilograms of weight loss. The patients in the intervention groups were asked to not increase their physical activity. The control intervention was best-practice care using the United Kingdom National Institute for Clinical Excellence guidelines. The authors report outcomes data after 1 year in the program. Twenty-one (14%) of the intervention patients did not complete the 12-month assessment compared with 2 (1%) of the control patients. At the final assessment, 36 intervention patients (24%) had lost at least 15 kilograms compared with none of the control patients. Diabetes remission, as defined as a hemoglobin A1C level of less than 6.5% (48 mmol/mol) after at least 2 months off all antidiabetic medications, was achieved in 45% of intervention patients compared with 4% of control patients (number needed to treat = 3; 95% CI 2 - 4). The authors also report that quality of life improved in the intervention group and deteriorated in the control group. Approximately 20% of the patients dropped out of the intervention, and 4% of the intervention participants reported serious adverse events (including biliary colic) compared with 1% of control participants (number needed to treat to harm = 30). It is unclear if the benefit persists 5 years after resuming food. Although the study was government funded, the Counterweight Plus website suggests that there is potential economic gain for those who deliver the service (http://www.counterweight.org/What-We-Offer/Health-Professionals-151).
Bottom line: After 12 months of an intensive weight-magaement program that included caloric-restricted dietary replacement followed by re-introduction of food, nearly half of the obese patients with type 2 diabetes achieved remission. The sustainability of this is uncertain. (LOE = 2b)
Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet 2018;391(10120):541-551

15. Liberal oxygen administration increases mortality for hospitalized patients

BACKGROUND: Administration of supplemental oxygen is generally perceived to be essentially harmless and potentially beneficial. In the UK, oxygen is given to 34% of ambulance patients, 25% of ED patients and 15% of those admitted to the hospital, but in 50-84% of these cases oxygen exposure is considered excessive. Researchers have raised concerns about the potential harmful effects of excessive oxygen supplementation.
METHODS: These multinational authors, coordinated in New Zealand, reviewed the findings of 25 randomized controlled trials that compared outcomes in 16,037 acutely ill adults aged 28-76 (median 64, 64% male) exposed to liberal versus conservative oxygen therapy (median FiO2 0.52 vs. 0.21).
RESULTS: Exposure to liberal oxygen therapy was associated with an increased risk of in-hospital mortality (relative risk [RR] 1.21, 95% CI 1.03-1.43, p=0.02). 30-day mortality (RR 1.14, 95% CI 1.01-1.28, p=0.033) and mortality at longest follow-up (median three months) (RR 1.10, 95% CI 1.00-1.20, p=0.044). On pooling of the data, the absolute increase in mortality risk with liberal oxygen therapy was 1.1% in-hospital, 1.4% at 30 days, and 1.2% at longest follow-up. There was no statistically significant difference between liberal and conservative oxygen therapy for the outcomes of development of hospital-acquired infections or hospital-acquired pneumonia, disability or the hospital length of stay.
CONCLUSIONS: The authors suggest that their review provides high-quality evidence that liberal oxygen therapy increases the risk of mortality in acutely ill adults.

Chu, D.K., et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA). Lancet 391(10131):1693, April 28, 2018

16. Calcium and vitamin D, alone or combined, do not reduce fracture risk in community-dwelling older adults

Clinical question: Does calcium and vitamin D, alone or in combination, reduce the risk of fracture in community-dwelling older adults?
Study design: Meta-analysis (randomized controlled trials) **Funding source:** Foundation
Setting: Various (meta-analysis)
Synopsis: These investigators thoroughly searched multiple databases, including PubMed, the Cochrane Library, Embase, and published systematic reviews without language restrictions for randomized trials comparing calcium, vitamin D, or both, with placebo or no treatment for fracture incidence in community-dwelling adults 51 years or older. Unpublished data were included where available. Two reviewers independently assessed published studies for inclusion criteria and methodologic quality using a standard risk-of-bias scoring tool. Disagreements were resolved by consensus. A total of 33 randomized controlled trials (N = 51,145) met inclusion criteria. Of these, 1 trial was low quality, 6 were high quality, and the remainder were moderate quality. Calcium and vitamin D, alone or in combination, did not significantly reduce the risk of hip, vertebral, nonvertebral, or total fractures. Formal subgroup analyses showed that the results were no different on the basis of calcium or vitamin D dosage, patient sex, fracture history, dietary calcium intake, and baseline serum 25-hydroxyvitamin D concentration. Vitamin D alone significantly increased the risk of hip fracture in the subgroup with baseline vitamin D concentrations of 20 ng/mL or greater. A formal analysis of publication bias was not performed because of the low number of published trials.
Bottom line: The use of calcium and vitamin D, alone or in combination, did not significantly reduce the risk of hip, vertebral, nonvertebral, or total fractures in community-dwelling older adults. Results were unchanged based on calcium or vitamin D dosage, patient sex, fracture history, dietary calcium intake, and baseline serum 25-hydroxyvitamin D concentration. Of specific concern: Vitamin D alone significantly increased the risk of hip fracture in the subgroup with baseline vitamin D concentrations of 20 ng/mL or greater and did not reduce the risk of hip fractures in those with concentrations less than 20 ng/mL. (LOE = 1a)
Zhao JG, Zeng XT, Wang J, Liu L. Association between calcium and vitamin D supplementation and fracture incidence in community-dwelling older adults. A systematic review and meta-analysis. JAMA 2017;318(24):2466-2482.

Acute Respiratory Tract Infections

John Hickner, MD
written by Mark H. Ebell MD, MS

Objectives

1. Summarize the latest evidence on sore throat, including use of steroids and ibuprofen lozenges
2. Learn the latest information about more accurate diagnosis of bacterial sinusitis, mono, and pertussis
3. Learn strategies for antibiotic stewardship

Sore throat

Here is a novel therapy that reduces sore throat pain.

1. POEM: Low-dose ibuprofen throat lozenge effective for sore throat pain

Clinical question: Is a 25-mg ibuprofen throat lozenge effective in reducing sore throat pain in adults?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (primary care)
Synopsis: Oral ibuprofen, 400 mg to 800 mg, is effective for sore throat pain, but the efficacy of a low-dose 25-mg ibuprofen throat lozenge was uncertain. These investigators identified adults, 18 years or older, who presented for an acute sore throat of 72 hours or less and a pain score on swallowing of at least 60 mm on a 0 to 100 mm visual analogue throat pain intensity scale. Eligible patients (N = 385) randomly received (uncertain allocation concealment) either ibuprofen 25 mg or matched placebo lozenge. Patients were instructed to suck one lozenge slowly until dissolution as needed for pain; up to six lozenges daily, with a minimal interval of at least 2 hours between lozenges. No other topical or systemic pain medications were allowed. Patients masked to treatment group assignment self-reported pain scores after every dose for up to 4 days. Complete follow-up occurred for 96.9% of patients for 4 days. Using intention-to-treat analysis, 33% and 50% pain-relief response rates up to 45 minutes after the first dose were significantly higher in the ibuprofen group than in the placebo group (number needed to treat = 8.0 and 11.5, respectively). Pain relief was also significantly higher for ibuprofen than placebo on the evening of the first day, but the differences in pain relief scores were no longer significant from day 2 onward.
Bottom line: Low-dose (25-mg) ibuprofen throat lozenges are more effective than placebo in reducing sore throat pain in adults for up to 24 hours.
Bouroubi A, Donazzolo Y, Donath F, et al. Pain relief of sore throat with a new anti-inflammatory throat lozenge, ibuprofen 25 mg: A randomised, double-blind, placebo-controlled, international phase III study. Int J Clin Pract 2017;71:e12961.

What about steroids? Some conflicting evidence from a positive Cochrane review and a large and less favorable randomized trial. Cochrane review including studies of varying quality, while trial excluded patients with most severe sore throat who are most likely to benefit.

2. POEM: Single-dose oral dexamethasone decreases sore throat pain (Cochrane review)

Clinical question: Do oral corticosteroids relieve pain in patients with acute sore throat?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: To determine whether an oral corticosteroid aids in symptom resolution, these researchers searched 4 databases, including Cochrane CENTRAL, trial registries, and reference lists of retrieved studies, and identified 10 studies of 1426 patients 5 years or older. Two reviewers independently selected the studies for inclusion and abstracted the data, selecting randomized controlled trials that compared 1 or 2 daily doses of corticosteroid with standard treatment or placebo in patients who presented to an emergency department or primary care office with clinical sore throat. Five studies evaluated oral dexamethasone and 3 studies evaluated a single intramuscular dose of dexamethasone, in addition to antibiotic treatment and analgesic treatment. Onset of pain relief was 4.8 hours faster with the steroid (7.4 vs 12.3 hours), with more than twice as many patients reporting complete resolution at 24 hours (relative risk 2.24; 95% CI 1.17 - 4.29). There was no demonstrated difference in days missed from school or work, and no difference in adverse effect rates between groups.
Bottom line: Sore throats are rarely fatal any more, but there is really no such thing as "just a sore throat." Whereas antibiotics have no analgesic activity, a single low-dose of a corticosteroid such as oral dexamethasone—0.6 mg per kg for children at least 5 years of age and up to 10 mg for adults—is effective in decreasing pain in the first 24 hours.
Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, et al. Corticosteroids for treatment of sore throat: systematic review and meta-analysis of randomised trials. BMJ 2017;Sep 20;358:j3887.

3. POEM: Dexamethasone may reduce sore throat symptoms in adults at 48 hours

Clinical question: Are oral steroids effective in the treatment of acute sore throat in adults?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: These investigators identified adults, 18 years or older, who presented to primary care offices in England with acute symptoms of sore throat and odynophagia for which the treating clinician did not prescribe immediate antibiotic therapy. Exclusion criteria included the recent use of inhaled or oral corticosteroids, recent adenotonsillectomy, recent use of antibiotics, or a clear alternative diagnosis such as pneumonia. Eligible participants (N = 565) randomly received (concealed allocation assignment) a single dose of dexamethasone (10 mg) or matching placebo. Treating clinicians could decide to offer no antibiotics (n = 349) or a delayed antibiotic (n = 227). Patients unaware of group assignment self-assessed outcomes including the primary outcome of complete resolution of sore throat symptoms at 24 hours. Secondary exploratory outcomes included complete resolution of sore throat at 48 hours, duration of moderately bad symptoms, time to onset of pain relief and time to complete resolution of symptoms, consumption of delayed antibiotic prescription, time missed from work or education, attendance at or telephone contact with any heath care facility because of the sore throat, and use of over-the-counter medications and/or other prescription medications in the first 7 days. Complete follow-up occurred for 94% of participants at 1 month. Using intention-to-treat analysis, no significant difference occurred among the steroid group and the placebo group in achieving complete resolution of symptoms at 24 hours. Results were similar between patients who were and were not offered a delayed antibiotic prescription. At 48 hours significantly more participants who received dexamethasone reported complete resolution of symptoms compared with those who received the placebo (35.4% vs 27.1%, respectively; NNT = 12; 7 - 146). Neither severity of sore throat at baseline nor a positive throat culture for Streptococcus bacteria on throat swab were related to group differences. No significant differences occurred between the treatment group and the placebo group in other secondary outcomes or serious adverse events.
Bottom line: A single dose of oral dexamethasone is no more effective than placebo in resolving acute sore throat symptoms at 24 hours in adults who do not receive immediate antibiotic therapy. However, among a multitude of exploratory secondary outcomes, the authors found that dexamethasone compared with placebo did increase the proportion of patients with symptom resolution at 48 hours (number needed to treat [NNT] = 12; 95% CI 7 - 146).
Hayward GN, Hay AD, Moore MV, et al. Effect of oral dexamethasone without immediate antibiotics vs placebo on acute sore throat in adults. A randomized clinical trial. JAMA 2017;317(15):1535-1543.

Palatine petechiae, splenomegaly, and posterior cervical, axillary and inguinal adenopathy are somewhat helpful in diagnosing acute mononucleosis. Most useful are posterior cervical, axillary, or inguinal adenopathy (LR+ 3) and either lymphocytosis and/or atypical lymphocytosis (LR 11 to 50).

4. POEM: Accurate signs, symptoms, and labs for diagnosing mononucleosis

Clinical question: Are there accurate signs, symptoms, and laboratory data for diagnosing infectious mononucleosis?
Study design: Diagnostic test evaluation
Setting: Population-based
Synopsis: These investigators systematically searched multiple sources including the Database of Abstracts of Review of Effectiveness, PubMed, EMBASE and bibliographies of relevant studies reporting data on the accuracy of symptoms, signs, and laboratory studies among patients with either a sore throat or who underwent testing for infectious mononucleosis. Inclusion criteria were consecutive enrollment or a convenience sample (no case-control studies); sufficient data to calculate sensitivity, specificity, and likelihood ratios; and a comparison of the index test with an adequate reference standard (eg, Epstein-Barr virus immunoglobulin test or heterophile antibody test). At least 2 individuals reviewed each study for inclusion and quality using a standard diagnostic studies scoring tool. Any discrepancies were resolved if needed by discussion with a third author. Three studies (n = 1388) included patients prospectively presenting with a sore throat, 3 retrospective studies (n = 2088) used laboratory data for patients suspected of mononucleosis, and 5 case series studies (n = 1293) enrolled patients with serologically confirmed mononucleosis. The absence of sore throat or headache (negative likelihood ratio [LR-] ranges = 0.51 - 0.62 and 0.63 - 0.73, respectively) were the most useful symptoms to reduce the likelihood of mononucleosis. Useful clinical signs for increasing the likelihood of the diagnosis included the presence of palatine petechiae (positive likelihood ratio [LR+] = 5.3; 95% CI 2.1-13), posterior cervical adenopathy (LR+ = 3.1; 1.6-5.9), and axillary or inguinal adenopathy (LR+ range = 3.0 - 3.1). The absence of any lymphadenopathy was most useful for reducing the likelihood of mononucleosis (LR- range = 0.23 - 0.44). Splenomegaly occurred in 7% to 53% of patients with mononucleosis (LR+ range = 1.9 - 6.6). Useful laboratory data included the presence of atypical lymphocytosis greater than or equal to 10% (LR+ = 11), with increasing likelihood with a greater percentage of atypical lymphocytes (LR+ = 26 for at least 20%, and LR+ = 50 for at least 40%). The presence of monocytosis also increased the likelihood of mononucleosis (LR+ range = 2.9 -14). The likelihood of mononucleosis was decreased with the presence of less than 10% atypical lymphocytes (LR- = 0.37; 0.26-0.51) and less than 35% lymphocytes overall (LR- = 0.22; 0.18-0.27).
Bottom line: Symptoms that reduce the likelihood of infectious mononucleosis include the absence of sore throat or headache. Clinical findings that increase the likelihood of infectious mononucleosis include palatine petechiae; splenomegaly; and posterior cervical, axillary, or inguinal adenopathy. Laboratory data that increase the likelihood of the diagnosis include an increasing percentage of lymphocytes with atypical lymphocytosis and monocytosis.
Ebell MH, Call M, Shinholser J, Gardner J. Does this patient have infectious mononucleosis? The rational clinical examination systematic review. JAMA 2016;315(14):1502-1509

Sinusitis

5. Cochrane: Antibiotics for acute maxillary sinusitis in adults

Background: Sinusitis is one of the most common diagnoses among adults in ambulatory care, accounting for 15% to 21% of all adult outpatient antibiotic prescriptions. However, the role of antibiotics for sinusitis is controversial.
Objectives: To assess the effects of antibiotics in adults with acute maxillary sinusitis by comparing antibiotics with placebo, antibiotics from different classes and the side effects of different treatments.
Search methods: We searched CENTRAL 2013, Issue 2, MEDLINE (1946 to March week 3, 2013), EMBASE (1974 to March 2013), SIGLE (OpenSIGLE, later OpenGrey (accessed 15 January 2013)), reference lists of the identified trials and systematic reviews of placebo-controlled studies. We also searched for ongoing trials via ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). We imposed no language or publication restrictions.
Selection criteria: Randomised controlled trials (RCTs) comparing antibiotics with placebo or antibiotics from different classes for acute maxillary sinusitis in adults. We included trials with clinically diagnosed acute sinusitis, confirmed or not by imaging or bacterial culture.
Data collection and analysis: Two review authors independently screened search results, extracted data and assessed trial quality. We calculated risk ratios (RRs) for differences between intervention and control groups in whether the treatment failed or not. All measures are presented with 95% confidence intervals (CIs). We conducted the meta-analyses using either the fixed-effect or random-effects model. In meta-analyses of the placebo-controlled studies, we combined data across antibiotic classes. Primary outcomes were clinical failure rates at 7 to 15 days and 16 to 60 days follow-up. We used GRADEpro to assess the quality of the evidence.
Main results: We included 63 studies in this updated review; nine placebo-controlled studies involving 1915 participants (seven of the studies clearly conducted in primary care settings) and 54 studies comparing different classes of antibiotics (10 different comparisons). Five studies at low risk of bias comparing penicillin or amoxicillin to placebo provided information on the main outcome: clinical failure rate at 7 to 15 days follow-up, defined as a lack of full recovery or improvement, for participants with symptoms lasting at least seven days. In these studies antibiotics decreased the risk of clinical failure (pooled RR of 0.66, 95% CI 0.47 to 0.94, 1084 participants randomised, 1058 evaluated, moderate quality evidence). However, the clinical benefit was small. Cure or improvement rates were high in both the placebo group (86%) and the antibiotic group (91%) in these five studies. When clinical failure was defined as a lack of full recovery (n = five studies), results were similar: antibiotics decreased the risk of failure (pooled RR of 0.73, 95% CI 0.63 to 0.85, high quality evidence) at 7 to 15 days follow-up. Adverse effects in seven of the nine placebo-controlled studies (comparing penicillin, amoxicillin, azithromycin or moxicillin to placebo) were more common in antibiotic than in placebo groups (median of difference between groups 10.5%, range 2% to 23%). However, drop-outs due to adverse effects were rare in both groups: 1.5% in antibiotic groups and 1% in control groups. In the 10 head-to-head comparisons, none of the antibiotic preparations were superior to another. However, amoxicillin-clavulanate had significantly more drop-outs due to adverse effects than cephalosporins and macrolides.
Author's Conclusions: There is moderate evidence that antibiotics provide a small benefit in immunocompetent primary care patients with uncomplicated acute sinusitis. However, about 80% of participants treated without antibiotics improved within two weeks. Clinicians need to weigh the small benefits of antibiotic treatment against the potential for adverse effects at both the individual and general population levels.
Ahovuo-Saloranta A, Rautakorpi U, Borisenko OV, Liira H, Williams Jr JW, Mäkelä M. Antibiotics for acute maxillary sinusitis in adults. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD000243.

6. Chronic sinusitis: saline irrigation helps somewhat; steroid doesn't add more benefit

Clinical question: In patients with chronic rhinosinusitis, does the addition of budesonide to a saline irrigation solution result in further improvement in symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: These researchers recruited 80 patients with chronic rhinosinusitis (2 or more symptoms, including mucopurulent drainage, nasal obstruction, facial pain, and decreased sense of smell at least 12 weeks) to be randomized, allocation concealment unknown, to receive treatment using a large-volume saline sinus irrigation with either placebo or budesonide 1 mg once daily for 30 days. The patients, average age 51 years, had a Sino-Nasal Outcome Test (SNOT-22) score of 44.1 out of a possible 110. A significant number of patients dropped out (23%), leaving 61 to be evaluated. The average decrease in scores was 20.7 points in the treated group and 13.6 points in the control group, which was not statistically significant. More participants in the treated group (79%) received a clinically important benefit of at least a 9-point improvement than in the saline-only group (59%; not statistically different). This small study, with significant dropouts, did not have the power to find a difference if one exists. I'm a little grumpy that the authors did not give specific data to judge the degree of benefit beyond a 9-point improvement for the responders.
Bottom line: This study showed that patients with chronic rhinosinusitis who continue to use a saline nasal wash (NeilMed) will often experience an improvement in symptoms that can be clinically meaningful, but the addition of the corticosteroid budesonide has yet to be shown to provide extra benefit.
Tait S, Kallogjeri D, Suko J, Kukuljan S, Schneider J, Piccirillo JF. Effect of budesonide added to large-volume, low-pressure saline sinus irrigation for chronic rhinosinusitis. A randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2018;144(7):605-612.

Cough, chest cold, and "acute bronchitis"

Among outpatients with cough for more than a week or two, about 12% in primary care and 18% of children had pertussis. In patients with community acquired pneumonia, about 10% had mycoplasma

and 3% legionella (Marchello C. Ann Fam Med 2016;14:552– 66). As with mono, clinical diagnosis of pertussis is of limited value. The most valuable “test”? Your gut (LR+ 3.3, LR- 0.63).

7. POEM: Typical signs and symptoms minimally effective for the diagnosis of pertussis infection

Clinical question: Are the typical signs and/or symptoms useful to accurately diagnose Bordetella pertussis infections in children and adults?
Study design: Systematic review
Setting: Various (meta-analysis)
Synopsis: Pertussis is much more common than many clinicians realize, with an overall prevalence of 12.4% (1 in 8) and 18% (1 in 5.5) among adults and children, respectively, with prolonged cough (greater than one week) seen in primary care settings. These investigators, including that Georgian Demon, thoroughly searched MEDLINE and reference lists of pertinent studies for prospective cohort studies of patients presenting with acute cough, prolonged cough, or clinically suspected pertussis. Inclusion criteria included the use of an acceptable reference test on all patients (e.g. PCR, culture, or serology). No restrictions applied to language, age, or immunization status. Two investigators independently evaluated all studies for inclusion criteria and methodologic quality using standard scoring tools. Discrepancies were resolved by consensus discussion with a third investigator. Studies using only single, non-paired, serology were considered to have a high risk of bias. A total of 22 studies (n=15,909) met inclusion criteria, including 14 judged at low risk, 4 at moderate risk, and 4 at high risk of bias. The overall clinical assessment by the evaluating clinician was most useful at ruling in pertussis (LR+ = 3.3; LR- = 0.63). Other typical symptoms including whooping cough, posttussive vomiting, paroxysmal cough, sputum, and disturbed sleep all had likelihood ratios of minimal, if any, diagnostic value (between 2.1 and 0.58). In children, whooping cough was more accurate for diagnosing pertussis than in adults (LR+ = 2.9 vs 1.9, respectively).
Bottom line: Bordetella pertussis (BP) is often the cause of cough lasting longer than 1 week in primary care settings. The overall clinical assessment by the evaluating clinician is most useful for accurately diagnosing BP infection. Other individual symptoms, including whooping cough, posttussive vomiting, and paroxysmal cough, are minimally, if at all, accurate for diagnosing BP.
Ebell MH, Marchello C, Callahan M. Clinical diagnosis of Bordetella pertussis infection: A systematic review. J Am Board Fam Med 2017;30(3):308-319.

What about steroids for patients with LRTI who do not have asthma? Don’t you wish it worked and was safe?

8. POEM: Oral steroids not helpful for acute lower respiratory tract infection in nonasthmatic adults

Clinical question: Are steroids useful in the treatment of acute lower respiratory tract infection in adults without asthma?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: Because symptoms of acute LRTI can mimic those of exacerbated asthma, steroids are commonly prescribed with or without antibiotics. These investigators enrolled adults, 18 years or older, presenting with an acute cough (lasting 28 days or less) as the main symptom and at least 1 other lower respiratory tract symptom (eg, phlegm, chest pain, wheezing, or shortness of breath). Exclusion criteria included evidence of chronic pulmonary disease, having received any asthma medication in the previous 5 years, or requiring same day hospitalization or urgent antibiotic treatment. Patients (N = 401) randomly received (concealed allocation assignment) either 40 mg prednisolone daily for 5 days or matched placebo. Those patients also receiving a nonurgent antibiotic prescription were asked to delay filling the prescription for at least 48 hours. Patients assessed outcomes using symptom diaries and remained masked to their treatment group assignment. Symptoms were measured daily, including twice-daily peak expiratory flow, for 28 days or until symptom resolution. Complete follow-up occurred for 94% of patients at 28 days. Using intention-treat analysis, no clinically significant group differences occurred in the median duration of cough or severity of symptoms, symptom duration, antibiotic use, peak flow, or patient satisfaction. There were also no significant subgroup effect differences (ie, smoking, wheezing, chest pain, or shortness of breath).
Bottom line: This study found no clinically significant benefit of steroids for the treatment of acute lower respiratory tract infection (LRTI) in adults without asthma, including those presenting with wheezing or shortness of breath.
Hay AD, Little P, Harnden A, et al. Effect of oral prednisolone on symptom duration and severity in nonasthmatic adults with acute lower respiratory tract infection. A randomized clinical trial. JAMA 2017;318(8):721-730.

So let’s STOP giving steroids to everyone. They are appropriate for patients with a history of asthma or COPD, but not for everyone who is coughing. What about cough medicines? Nothing seems to work very well.

9. POEM: Nothing works for cough associated with the common cold

Clinical question: Which treatments are safe and effective for cough associated with the common cold?
Study design: Systematic review
Setting: Other
Synopsis: Although billed as an "expert panel report," this was really a hybrid of a systematic review, an "umbrella review" of published systematic reviews, and a guideline. The authors did a careful literature search, identifying randomized controlled trials (RCTs), as well

as previous systematic reviews, and updated the searches of the published systematic reviews. They included any randomized trial of any treatment for acute cough in patients with an upper respiratory tract infection or the common cold. Although the authors said they looked for studies of herbal supplements, and included a few of them, the Cochrane Review of pelargonium sidioides was not included. The studies were assessed for quality using the Cochrane Risk of Bias tool for RCTs and a similar tool for systematic reviews, and excluded any studies at high risk of bias. The expert panel reviewed the evidence, then made 4 key recommendations. They concluded that there was insufficient evidence to make a recommendation for acetylcysteine or carbocysteine, and they recommend against the use of over-the-counter cold medications available in the United States to treat cough. They also recommend against the use of nonsteroidal anti-inflammatory drugs, given their lack of proven efficacy and, of course, their potential harms. Honey gets some love: The authors conclude that for children older than 1 year and adolescents with cough, honey is probably better than placebo or diphenhydramine, but not any better than dextromethorphan (…which they just told us not to use). Zinc had mixed evidence, and some of the benefit was attributed to underlying zinc deficiency in some countries, as well as the difficulty in masking patients to the treatment. In the end, the panel did not recommend the use of zinc. They also found no good evidence supporting or refuting the benefits of over-the-counter antitussives, expectorants, mucolytics, antihistamines, or combinations of any of them. Finally, the panel recommends against using codeine-containing medications in children.
Bottom line: Suck it up: you have a cold, it'll get better. That seems to be the bottom line from this expert panel report, which found little evidence of benefit for most commonly used medications for the self-limited condition of the common cold. Ultimately, physicians must often act in the absence of good evidence, and it is reasonable to recommend safe options for the treatment of cough even if the optimal evidence is not available. These treatments include honey, dextromethorphan, and possibly zinc for patients with cough.
Malesker MA, Callahan-Lyon P, Ireland B, Irwin RS, CHEST Expert Cough Panel. Pharmacologic and nonpharmacologic treatment for acute cough associated with the common cold: CHEST Expert Panel Report. Chest 2017;152(5):1021-1037.

10. POEM: Subacute cough treatments: limited data, unclear benefits

Clinical question: Which treatments for subacute cough are effective?
Study design: Systematic review
Setting: Outpatient (any)
Synopsis: Subacute cough—defined as cough that lasts no more than 8 weeks, is not accompanied by radiographic evidence of pneumonia, and resolves on its own—is fairly common, especially following respiratory infections. These authors systematically searched PubMed and the Cochrane Central Register of Clinical Trials to identify randomized trials published in English that evaluated various treatments in patients at least 16 years old with subacute cough. The studies could have included drug and nondrug treatments, but excluded Chinese or Asian herbal remedies. They also hand-searched reference lists of included studies, relevant systematic reviews, and clinical practice guidelines. Two authors independently assessed the inclusion of studies and the risk of bias for each study. They used a third author to resolve disagreements. They were able to find only 6 trials with between 30 and 276 patients (median = 96). The studies included montelukast, inhaled albuterol (also called salbutamol) plus ipratropium, gelatin, inhaled corticosteroids (fluticasone propionate, budesonide), and opioids. Five of the studies compared treatment with placebo, one with usual care. Overall, the reporting of the studies made assessing their risk of bias difficult. The studies used a variety of cough severity scores. Although the authors identified statistically significant improvement of cough scores with some interventions, none were clinically important. Additionally, some interventions provided short-term improvement, but none were sustained beyond 2 weeks. Five studies reported on adverse effects of treatment, which were mostly mild and ranged from 0% to 40% for active treatment and 0% to 27% for placebo or usual care.
Bottom line: The available evidence for treating patients with subacute cough is limited and fails to demonstrate meaningful improvements.
Speich B, Thomer A, Aghlmandi S, Ewald H, Zeller A, Hemkens LG. Treatments for subacute cough in primary care: systematic review and meta-analyses of randomised clinical trials. Br J Gen Pract 2018;68(675):e694-e702.

11. Cochrane: Antibiotics for acute bronchitis

Background: The benefits and risks of antibiotics for acute bronchitis remain unclear despite it being one of the most common illnesses seen in primary care.
Objectives: To assess the effects of antibiotics in improving outcomes and to assess adverse effects of antibiotic therapy for people with a clinical diagnosis of acute bronchitis.
Search methods: We searched CENTRAL 2016, Issue 11 (accessed 13 January 2017), MEDLINE (1966 to January week 1, 2017), Embase (1974 to 13 January 2017), and LILACS (1982 to 13 January 2017). We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 5 April 2017.
Selection criteria: Randomised controlled trials comparing any antibiotic therapy with placebo or no treatment in acute bronchitis or acute productive cough, in people without underlying pulmonary disease.
Data collection and analysis: At least two review authors extracted data and assessed trial quality.
Main results: We did not identify any new trials for inclusion in this 2017 update. We included 17 trials with 5099 participants in the primary analysis. The quality of trials was generally good. At follow-up there was no difference in participants described as being clinically improved between the antibiotic and placebo groups (11 studies with 3841 participants, risk ratio (RR) 1.07, 95% confidence interval (CI) 0.99 to 1.15). Participants given antibiotics were less likely to have a cough (4 studies with 275 participants, RR 0.64, 95% CI 0.49 to 0.85; number needed to treat for an additional beneficial outcome (NNTB) 6) and a night cough (4 studies with 538 participants, RR 0.67, 95% CI 0.54 to 0.83; NNTB 7). Participants given antibiotics had a shorter mean cough duration (7 studies with 2776 participants, mean difference (MD) -0.46 days, 95% CI -0.87 to -0.04). The differences in presence of a productive cough at follow-up and MD of productive cough did not reach statistical significance.

Antibiotic-treated participants were more likely to be improved according to clinician's global assessment (6 studies with 891 participants, RR 0.61, 95% CI 0.48 to 0.79; NNTB 11) and were less likely to have an abnormal lung exam (5 studies with 613 participants, RR 0.54, 95% CI 0.41 to 0.70; NNTB 6). Antibiotic-treated participants also had a reduction in days feeling ill (5 studies with 809 participants, MD -0.64 days, 95% CI -1.16 to -0.13) and days with impaired activity (6 studies with 767 participants, MD -0.49 days, 95% CI -0.94 to -0.04). The differences in proportions with activity limitations at follow-up did not reach statistical significance. There was a significant trend towards an increase in adverse effects in the antibiotic group (12 studies with 3496 participants, RR 1.20, 95% CI 1.05 to 1.36; NNT for an additional harmful outcome 24).
Authors' conclusions: There is limited evidence of clinical benefit to support the use of antibiotics in acute bronchitis. Antibiotics may have a modest beneficial effect in some patients such as frail, elderly people with multimorbidity who may not have been included in trials to date. However, the magnitude of this benefit needs to be considered in the broader context of potential side effects, medicalisation for a self -imiting condition, increased resistance to respiratory pathogens, and cost of antibiotic treatment.
Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD000245. DOI: 10.1002/14651858.CD000245.pub4.

Antibiotic stewardship

We've been recommending delayed antibiotic prescriptions for a while now. Do they cause any harms, though? Turns out patients don't mind, and it might even reduce re-consultation.

12. POEM: Delayed Rx for respiratory infections produces similar results and satisfaction as immediate treatment

Clinical question: In patients with respiratory tract infections (bronchitis, sinusitis, pharyngitis), is a delayed prescription strategy as effective as immediate treatment and as accepted by patients?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: These researchers evaluated 398 adults with acute, uncomplicated respiratory infections from 23 primary care centers in Spain. The patients had acute pharyngitis (46%), acute bronchitis (32%), rhinosinusitis (20%), or exacerbation of mild-to-moderate chronic obstructive pulmonary disease (2%). The physicians had "reasonable doubt as to whether to treat with an antibiotic." Patients were, on average, on the younger side (mid-40s), half were smokers or former smokers, almost no patients (< 2%) were febrile, and they reported mild to moderate symptoms for an average of 6 days. Patients were randomized, using concealed allocation, to 1 of 4 potential prescription strategies. One group was given an antibiotic to begin at once; 2 groups were given a delayed prescription, either a "take and hold prescription" or a "come back and pick up, if necessary prescription"; and the final group was not given any prescription. The average duration of symptoms was significantly longer in patients not given a prescription as compared with patients given an immediate antibiotic, with the duration in patients given delayed prescriptions somewhere in between but not significantly different from the immediate prescription. The duration of moderate or severe symptoms was lessened significantly with immediate treatment as compared with delayed prescriptions, but the average difference in duration was 0.5 day to 1.0 day. Patients in the delayed prescription groups experienced fewer days absent from work or unable to do their daily activities. Patient satisfaction was similar across all groups. Prescription use was decreased by two-thirds with the delayed prescription approaches.
Bottom line: In almost 400 Spanish primary care patients with mild to moderate symptoms of respiratory infection of less than 1 week's duration, both a "take-and-hold" prescription and a "come back and pick up, if necessary" prescription produced a similar clinical response -- and similar patient satisfaction score -- as immediate antibiotic treatment, while decreasing overall antibiotic use. Other studies of this patient population have shown that patients prefer the security of a prescription, delayed or not, over withholding antibiotic treatment. The effect of legitimizing an illness by awarding a prescription should not be underestimated.
de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, et al, for the Delayed Antibiotic Prescription (DAP) Group. Prescription strategies in acute uncomplicated respiratory infections. A randomized clinical trial. JAMA Intern Med 2016;176(1):21-29.

13. POEM: Delayed antibiotic prescription for new-onset cough associated with decreased re-consultation

Clinical question: In adults with lower respiratory tract infection, what is the effect of different antibiotic prescribing strategies?
Study design: Cohort (prospective)
Setting: Outpatient (primary care)
Synopsis: This study included adult patients seen in United Kingdom primary care offices who had acute cough for 3 weeks or less that was judged by their physician to be due to infection. Follow-up was 99.6% of patients. Of the 28,779 patients not immediately referred for hospitalization or radiographic investigation, 25.5% were not treated with an antibiotic, 61.3% received a prescription for an antibiotic, and 13.3% received a prescription for delayed antibiotic (average advised delay was 3 days). This was not a randomized study and physicians were selective in their use of antibiotics, prescribing immediate antibiotic for patients who were older; had major comorbidities; reported more shortness of breath, fever, or purulent sputum; or had low oxygen saturation, higher severity, and crackles or wheeze. Subsequently, hospitalization or death occurred in 0.3% after no antibiotic, 0.9% after immediate antibiotic treatment, and 0.4% after delayed antibiotic (no statistically significant difference). Follow-up visits were common in all groups but were significantly reduced by delayed antibiotic treatment (14.1% with delayed antibiotic vs 19.7% with no antibiotic and 25.3% with immediate antibiotic).
Bottom line: Delayed antibiotic treatment (that is, giving a prescription with a suggestion to fill it only if symptoms are still present after 3 days) was associated with decreased revisits by adults with new-onset cough deemed to be infective. Neither immediate nor delayed antibiotic treatment altered hospitalization rates, but this lack of difference might be due to appropriately selective prescribing of

antibiotics to more at-risk patients. In this study, 1 in 4 patients were not prescribed antibiotic treatment and they fared as well as the patients who received a prescription.
Little P, Stuart B, Smith S, et al. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. BMJ 2017;357:j2148.

The next study looked at 3 interventions: an automated alternative treatment suggestions when providers attempted to prescribe antibiotics for antibiotic-inappropriate diagnoses; requiring providers to text an "antibiotic justification note" that became a permanent part of the medical record; or distributing periodic emails to participating providers labeling them as either a "top performer" or "not a top performer" by comparing their antibiotic prescribing behavior with their peers'.

14. POEM: Behavioral interventions reduce inappropriate antibiotic prescribing for acute RTIs

Clinical question: Do behavioral interventions reduce rates of inappropriate antibiotic prescribing for acute respiratory tract infections in primary care?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (primary care)
Synopsis: Clinical guidelines encourage avoiding antibiotics for infections when treatment is of minimal, if any, benefit. However, inappropriate antibiotic prescribing for acute respiratory tract infections persists. These investigators invited 49 practices in Massachusetts and California (N = 243 clinicians) to receive various combinations of behavioral interventions aimed at reducing inappropriate antibiotic prescribing. The first intervention used automated alternative treatment suggestions when providers attempted to prescribe antibiotics for antibiotic-inappropriate diagnoses. A second intervention required providers to text an "antibiotic justification note" that became a permanent part of the medical record. The third intervention distributed periodic emails to participating providers labeling them as either a "top performer" or "not a top performer" by comparing their antibiotic prescribing behavior with their peers'. Providers included internists (60%), nurse practitioners/physician assistants (19%), and family physicians (13%). The study excluded patients with chronic medical conditions that necessitate more frequent antibiotic prescriptions for acute respiratory tract infections (eg, emphysema). Practices were randomized to receive 0, 1, 2, or all 3 interventions for 18 months and no cases were lost to follow-up. Not surprisingly, the control group significantly decreased inappropriate antibiotic prescribing rates (11% absolute reduction) during the study period. This is known as the Hawthorne effect: changing your behavior simply because you know you're being observed. Both the accountable justification and peer comparison interventions significantly decreased antibiotic prescribing rates compared with the control group (-7.0% and -5.2%, respectively). However, the suggested alternatives intervention did not significantly reduce antibiotic prescribing rates compared with control. The latter result is disheartening but consistent with prior findings about influencing clinical decision making: Information alone rarely changes behavior. The most powerful influence continues to be peer pressure and the desire to conform. Please attribute the authorship of this POEM to Patrick L. Turner, MD, Fellow, Department of Family Medicine, The University of Virginia, Charlottesville, VA.
Bottom line: Requiring clinicians to justify antibiotic prescribing in the permanent electronic health record and to undergo periodic peer comparisons of prescribing rates are both effective interventions for reducing inappropriate antibiotic prescribing for acute respiratory tract infections. Helpful reminders and suggested treatment alternatives do not reduce inappropriate prescribing rates. Information alone rarely changes behavior, but the desire to conform with our peers can be very persuasive.
Meeker D, Linder JA, Fox CR, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices. JAMA 2016;315(6):562-570.

When you prescribe an antibiotic, prescribe a shorter rather than a longer course for acute respiratory infections and UTIs.

15. Short courses of antibiotics as effective as longer courses for outpatient infections

Clinical question: Are short courses of antibiotics as effective as longer courses for common outpatient infections?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: This is a relatively new kind of study: a systematic review of systematic reviews, also called a systematic overview. The authors searched 5 databases and identified 9 systematic reviews that compared the duration of antibiotic therapies for a common outpatient infection. The reviews included between 2 studies and 17 studies, with a total of between 395 and 5763 patients. The best studied conditions were urinary tract infection (UTI), sinusitis, and community-acquired pneumonia (CAP). The authors found that, in children, 5 to 7 days was as good as 10 days for strep pharyngitis; 3 days was as good as 5 days for CAP; more than 2 days was as good as 7 or more days for otitis media, and 2 to 4 days was as good as 7 to 14 days for UTI. In adults, 3 to 7 days was as good as 6 to 10 days for acute bacterial sinusitis, 3 days was as good as 5 or more days for uncomplicated UTI in nonpregnant women, and 7 to 14 days was as good as 14 to 42 days for acute pyelonephritis. The authors also found that 7 or fewer days was as good as more than 7 days for CAP, and 3 to 6 days was as effective as 7 to 14 days for UTI in older women. There was some evidence that shorter courses resulted in fewer adverse events when treating acute otitis media in children and acute sinusitis in adults.
Bottom line: Just about every time someone asks "Can I get away with a shorter course of antibiotics," the answer is "Yes, you can." Shorter courses reduce cost and may reduce the likelihood of adverse events.

Dawson-Hahn EE, Mickan S, Onakpoya I, et al. Short-course versus long-course oral antibiotic treatment for infections treated in outpatient settings: a review of systematic reviews. Fam Pract 2017;34(5):511-519.

Bottom Lines

1. Anti-inflammatory lozenges may be helpful for sore throat.
2. Dexamethasone is of limited benefit, if any, for sore throat.
3. Steroids do nothing for acute bronchitis in patients without asthma, and antibiotics decrease symptom duration about a half day on average.
4. Nothing works very well for acute and subacute cough.
5. Behavioral interventions and delayed prescriptions can reduce antibiotic use for acute RTI.
6. When you choose to prescribe an antibiotic, use shorter courses (3 to 5 days) for acute respiratory infections and acute cystitis.