Syllabus for Essential Evidence Conference
North Dakota Academy of Family Physicians
January 19, 2026

Learning Objectives

Discuss recent research important to family physicians and other primary care clinicians for updating their approaches to common medical conditions. Objectives for each presentation are listed at the beginning of each talk. Each talk is based on a literature review of recent research studies. Evidence sources include InfoPOEMs®, PubMed and Cochrane systematic reviews.

Faculty

Henry C. Barry, MD, MS is a Professor Emeritus of Family Medicine in the College of Human Medicine at Michigan State University. After graduating from the University of Maryland, he completed his family medicine residency at St. Lawrence Hospital in Lansing, Michigan and completed a master's in Clinical Research Design and Statistical Analysis at the University of Michigan School of Public Health. For over 25 years, as one of the original "POETs," he and colleagues have generated over 6000 POEMs – Patient Oriented Evidence that Matters – short critical summaries of original research on topics relevant to primary care physicians.

Mark H. Ebell MD, MS is Deputy Editor of American Family Physician and Editor-in-Chief of Essential Evidence Plus. He is a graduate of the University of Michigan School of Medicine, a former RWJ Generalist Physician Faculty Scholar, and is former editor of the Journal of Family Practice. Dr. Ebell is author of 9 books and over 500 peer reviewed articles. From 2012 to 2016 he was a member of the USPSTF, and in 2019 he was a Fulbright Scholar at the Royal College of Surgeons in Ireland. Dr. Ebell is the 2024 Curtis Hames Award winner from STFM for lifetime contribution to primary care research.

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 since 1988. 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.

Kate Rowland, MD, MS is an associate professor and vice chair for education at Rush University. She just completed her term serving as the current President of the Illinois Academy of Family Physicians. She is also an associate medical editor for the American Academy of Family Physicians' FP Essentials series and for Essential Evidence. She is a graduate of Rush Medical College and completed post-graduate training at the Advocate Illinois Masonic Family Medicine residency and the University of Chicago primary care research fellowship.

Free podcast

Drs. Barry, Ebell, Ferenchick and Rowland produce a free commercial-free podcast, ***Primary Care Update***, where each presents a short summary of a recent study and the team discusses its validity and application. The podcasts are 25-30 minutes in length and are available at Spotify and most other podcast platforms. https://creators.spotify.com/pod/profile/primary-care-update

Faculty Disclosure Statements

Dr. Barry is paid by Wiley Publishing to generate content for Essential Evidence Plus.
Dr. Ebell is the paid editor for Essential Evidence Plus.
Dr. Ferenchick and Dr. Rowland have no relevant financial relationship or interest with a proprietary entity producing health care goods or services.

In memoriam

John Hickner helped found the Essential Evidence courses. His vision was to work closely with state academies of family physicians to deliver high quality, evidence-based CME. John practiced in Escanaba Michigan and served on the faculty in the College of Human Medicine at Michigan State University for many years before becoming Chair of Family Medicine at the Cleveland Clinic and then at University of Illinois at Chicago. He also served as the Editor-in-Chief for the Journal of Family Practice for over a decade. His dedication to practice-based research, rural medicine and the care of patients provided the basis for his national reputation. Sadly, John died in 2022. His family and friends have created a tribute fund at the College of Human Medicine. The fund will support a medical student from Michigan's Upper Peninsula who is interested in rural medicine and research. If you have been touched by John and would like to honor him, please go to https://givingto.msu.edu/gift/?sid=17374 to make a contribution.

Schedule

Monday, January 19			page
7:30-8:00	Intro, Screening & Prevention	Barry	3
8:00-8:30	Diabetes Update	Rowland	15
8:30-9:00	Guidelines You Can Trust	Barry	24
9:00-9:30	Depression & Anxiety	Rowland	32
	Ski slopes, other fun, or naps		
4:30-5:00	Liver and lower GI	Rowland	38
5:00-5:30	Neurology and headache update	Barry	45
5:30-6:00	Complementary and Alternative Medicine Update	Rowland	51
6:00-6:30	Top 20 POEMs	Barry	57

Screening and Prevention — Mark H. Ebell MD, MS

Questions we're going to answer:

1. What are pros and cons of different CRC screening tests, and starting at 45 vs 50 years?
2. What are the benefits and harms of starting screening mammography at age 40 instead of 45 years?
3. Is there a role for MRI and ultrasound in screening for breast cancer?
4. How beneficial is lung cancer screening?

First, though, what are POEMs and where can you get them?

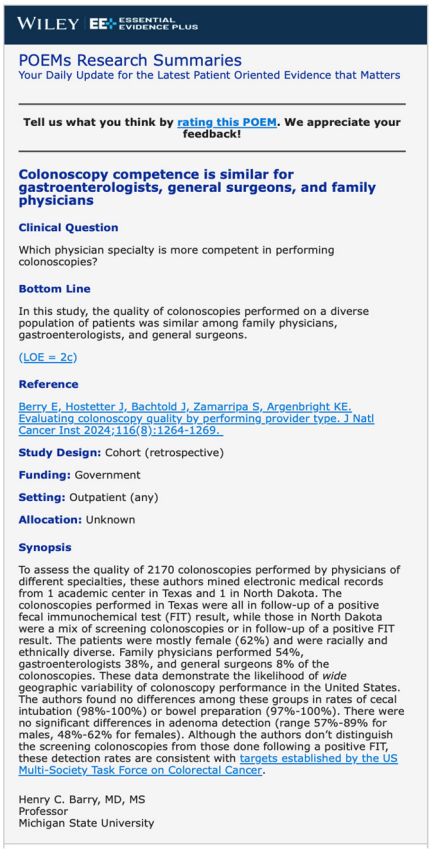
For 25 years, 6 of us (me, Dave Slawson, Allen Shaughnessy, Linda Speer, Nita Shrikant and Henry Barry) have reviewed 110 journals/month.

We identify studies with the potential to change practice because:

1. They address a primary care problem
2. They report improved patient-oriented evidence (not surrogate or disease-oriented endpoints)
3. They would require a change in practice

We summarize them in POEMs (Patient Oriented Evidence that Matters) and email them daily to subscribers. Learn more at http://www.essentialevidenceplus.com

You can also get 4 for free each month in *American Family Physician* journal and get our free "Primary Care Update" podcast on Apple Podcasts, Spotify, etc.



WILEY EE ESSENTIAL EVIDENCE PLUS

POEMs Research Summaries
Your Daily Update for the Latest Patient Oriented Evidence that Matters

Tell us what you think by rating this POEM. We appreciate your feedback!

Colonoscopy competence is similar for gastroenterologists, general surgeons, and family physicians

Clinical Question

Which physician specialty is more competent in performing colonoscopies?

Bottom Line

In this study, the quality of colonoscopies performed on a diverse population of patients was similar among family physicians, gastroenterologists, and general surgeons.

(LOE = 2c)

Reference

Berry E, Hostetter J, Bachtold J, Zamarripa S, Argenbright KE. Evaluating colonoscopy quality by performing provider type. J Natl Cancer Inst 2024;116(8):1264-1269.

Study Design: Cohort (retrospective)

Funding: Government

Setting: Outpatient (any)

Allocation: Unknown

Synopsis

To assess the quality of 2170 colonoscopies performed by physicians of different specialties, these authors mined electronic medical records from 1 academic center in Texas and 1 in North Dakota. The colonoscopies performed in Texas were all in follow-up of a positive fecal immunochemical test (FIT) result, while those in North Dakota were a mix of screening colonoscopies or in follow-up of a positive FIT result. The patients were mostly female (62%) and were racially and ethnically diverse. Family physicians performed 54%, gastroenterologists 38%, and general surgeons 8% of the colonoscopies. These data demonstrate the likelihood of *wide* geographic variability of colonoscopy performance in the United States. The authors found no differences among these groups in rates of cecal intubation (98%-100%) or bowel preparation (97%-100%). There were no significant differences in adenoma detection (range 57%-89% for males, 48%-62% for females). Although the authors don't distinguish the screening colonoscopies from those done following a positive FIT, these detection rates are consistent with targets established by the US Multi-Society Task Force on Colorectal Cancer.

Henry C. Barry, MD, MS
Professor
Michigan State University

Colorectal cancer screening

USPSTF recommendation statement

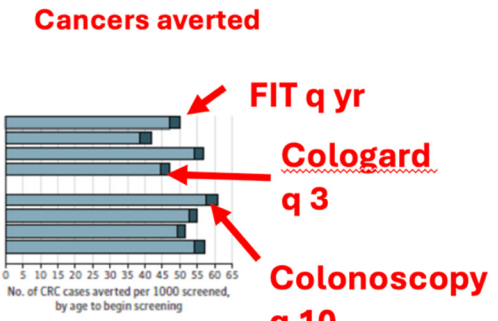
- Screen for colorectal cancer in adults aged 45-49 years (B recommendation).
- Screen for colorectal cancer in all adults aged 50 to 75 years (A recommendation)
- Screen for colorectal cancer in all adults aged 76 to 85 years (C recommendation)
- Use any of 7 tests including annual FIT, colonoscopy, Cologard,flex sig + FIT, or CT colonography

The recommendation to start at age 45 years is, um, interesting. While the USPSTF members say it is due to "new science", there have been no new clinical trials other than the one we'll discuss in a minute, and modeling results have not changed either. Here is a summary of benefits and harms by type of screening test

POTENTIAL BENEFITS

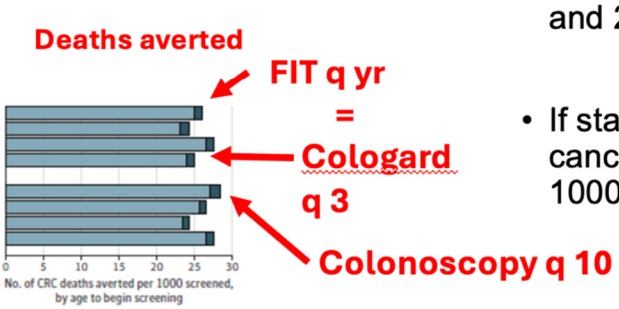
B Benefit: Estimated No. of CRC cases averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC cases averted if start screening[b] At age 50 y	At age 45 y	Additional CRC cases averted if start screening at age 45 y
Stool tests			
FIT every year	47	50	3
HSgFOBT every year[c,d]	39	42	3
sDNA-FIT every year	54	57	3
sDNA-FIT every 3 y[d]	44	47	3
Direct visualization tests			
COL every 10 y	58	61	3
CT colonography every 5 y	53	55	2
Flexible SIG every 5 y	49	51	2
Flexible SIG every 10 y plus FIT every year	54	57	3



C Benefit: Estimated No. of CRC deaths averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC deaths averted if start screening[b] At age 50 y	At age 45 y	Additional CRC deaths averted if start screening at age 45 y
Stool tests			
FIT every year	25	26	1
HSgFOBT every year[c,d]	23	24	1
sDNA-FIT every year	27	28	1
sDNA-FIT every 3 y[d]	24	25	1
Direct visualization tests			
COL every 10 y	27	28	1
CT colonography every 5 y	26	26	0.9
Flexible SIG every 5 y	23	24	0.9
Flexible SIG every 10 y plus FIT every year	26	28	1

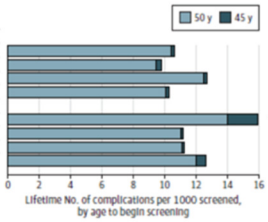


- Benefit is very similar across screening methods:
  - 45-60 fewer cancers/1000 (NNS ~ 20)
  - 25-28 fewer deaths/1000 (NNS ~ 39)
- Benefits for FIT = Cologuard
- Colonoscopy: 10 fewer cancers and 2 fewer deaths/1000 pop'n
- If start at 45: only 2-3 fewer cancers and 1 fewer death per 1000 persons

POTENTIAL HARMS

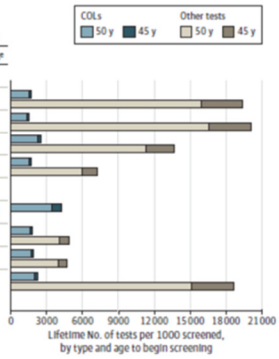
A Harms: Estimated lifetime number of complications (gastrointestinal and cardiovascular) of CRC screening and follow-up procedures per 1000 individuals screened[a]

Screening modality and frequency	Mean estimate of complications if start screening[b] At age 50 y	At age 45 y	Additional complications if start screening at age 45 y
Stool tests			
FIT every year	10	11	0.2
HSgFOBT every year[c,d]	9	10	0.3
sDNA-FIT every year	12	13	0.2
sDNA-FIT every 3 y[d]	10	10	0.3
Direct visualization tests			
COL every 10 y	14	16	2
CT colonography every 5 y	11	11	0.2
Flexible SIG every 5 y	11	11	0.1
Flexible SIG every 10 y plus FIT every year	12	13	0.6



B Burden: Estimated lifetime number of tests by type per 1000 individuals screened[a]

Screening modality and frequency	Mean estimate of lifetime No. of tests by type if start screening at age 50 y COLs	Other tests[e]	Mean estimate of lifetime No. of tests by type if start screening at age 45 y COLs	Other tests[e]	Additional tests if start screening at age 45 y by type COLs	Other tests[e]
Stool tests						
FIT every year	1496	15940	1682	19412	186	3472
HSgFOBT every year[c,d]	1347	16577	1535	20077	188	3501
sDNA-FIT every year	2221	11303	2531	13693	311	2390
sDNA-FIT every 3 y[d]	1477	6006	1661	7194	184	1188
Direct visualization tests						
COL every 10 y	3464	0	4248	0	784	No change
CT colonography every 5 y	1590	4056	1750	4859	161	803
Flexible SIG every 5 y	1660	3946	1840	4723	179	777
Flexible SIG every 10 y plus FIT every year	1953	15088	2224	18641	270	3553



Serious CV or GI complications

- Both FIT, Cologard: **10/1000**
- Colonoscopy: **15/1000**

Lifetime colonoscopies

- Both FIT, Cologard: **2 / lifetime**
- Colonoscopy: **4 to 5 / lifetime**

If starting at 45: 2 more serious complications (if colonoscopy first strategy) and ~ 1 more colonoscopy lifetime

You can also summarize the benefits and harms in a table, showing what would happen for 1000 persons screened over a lifetime:

Benefit / Burden/Harm

Picture	Colonoscopy q 10 years	FIT q year	Cologard q 3 years	Favors	Net Impact
CRC cases averted	61	50	47	Colonoscopy	11 fewer CRCs
CRC deaths averted	28	26	25	Colonoscopy	2 fewer CRC deaths
Lifetime colonoscopies	4.5	1.7	1.7	FIT	~3 fewer colonoscopies
GI and CV complications	16	10	10	FIT	6 fewer complications

In fact, the ACP advises that we consider **not** screening average-risk adults aged 45-49 years for colorectal cancer; it also says to stick to FIT or colonoscopy, and to **not** use CT colonography or Cologard

POEM #1: ACP guideline: consider NOT screening patients age 45 to 49 for colorectal cancer
Clinical question: When should we start screening for colorectal cancer, and how should it be done?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: This guidance from the American College of Physicians focused on how best to avoid premature death due to colorectal cancer (no screening test for colorectal cancer has been shown to reduce all-cause mortality) by screening adults at average risk (ie, those without a family history or other risks). The guidelines are based on a review of existing guidelines that provide discrepant recommendations. All guidelines except one were from North America, and all were less than 5 years old. The guidelines were evaluated using the Appraisal of Guidelines for Research & Evaluation (AGREE) II instrument. The guideline committee reported no financial conflicts of interest and, unusual for guideline developers, recused members with intellectual conflicts of interest. The working group included a patient representative. They considered benefits, risks, and costs in their recommendations (some groups, such as the United States Preventive Services Task Force, do not consider cost). The guideline continues to suggest beginning screening at age 50 years and stopping at age 75 years, or earlier if patients have a life expectancy of 10 years or less. They suggest not screening asymptomatic average-risk adults between the ages of 45 to 49 years; at the very least, benefits and harms of screening should be discussed before setting up screening. They continue to suggest presenting benefits, harms, costs, and frequency data to patients and letting them decide whether they want to be screened via (1) fecal immunochemical test (FIT) or high sensitivity guaiac-based fecal occult blood testing every 2 years; (2) colonoscopy every 10 years; or (3) flexible sigmoidoscopy every 10 years with FIT every 2 years. The guideline recommends against screening using stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer.
Bottom line: This guideline updates recommendations issued in a 2019 guideline from the same group, based on the publication of 2 new guidelines from other groups. There are 2 new recommendations. One is to consider not screening patients aged 45 to 49 years. The other recommendation is against screening using stool DNA, computed tomography colonography, capsule endoscopy, urine, or serum screening tests for colorectal cancer.
Qaseem A, Harrod CS, Crandall CJ, Wilt TJ, et al, for the Clinical Guidelines Committee of the American College of Physicians. Screening for colorectal cancer in asymptomatic average-risk adults: a guidance statement from the American College of Physicians (version 2). Ann Intern Med 2023;176(8):1092-1100.

This next study is a headscratcher. The USPSTF modelers (CISNet, 6 groups from around the world, allegedly the best of the best of the best, estimated the following benefits of a lifetime of CRC screening using colonoscopy (very similar for FIT and other methods):

Yet after a single colonoscopy and 10 years of follow-up, even the most optimistic interpretation of the NordICC trial was an absolute risk reduction of CRC mortality of 0.15% and NNS = 667. Admittedly it is a single screen and only 10 years, not 25 years of screening and lifetime follow-up…but nearly 20 fold less mortality reduction than USPSTF modeling? Hmmm…

POEM #2. Invitation to a single colonoscopy has only modest impact on colorectal cancer incidence

Clinical question: Does an invitation to colonoscopy reduce the incidence of colorectal cancer and colorectal cancer mortality compared with usual care?
Study design: Randomized controlled trial (single-blinded)
Setting: Population-based
Synopsis: Despite widespread use as a screening test for colorectal cancer (CRC) in the United States, colonoscopy has never been subjected to a randomized trial. These authors identified 94,959 healthy men and women, aged 55 to 64 years, from the Netherlands, Norway, Sweden, and Poland who had not previously been screened for CRC. None of these countries had organized programs for CRC screening using colonoscopy, at least not in the regions from which participants were recruited. Unfortunately, follow-up data for 10,374 Dutch participants could not be included because of changes in (overly) restrictive European data protection laws that made it impossible to obtain data for uninvited persons from the general population. The remaining 84,585 participants were randomized in a 1:2 ratio to receive an invitation to a single screening colonoscopy or usual care. The median age at enrollment was 59 years, half the participants were women, and most came from Poland or Norway. Colonoscopy was performed at dedicated centers with training and quality assurance programs.
Only 11,843 of the 28,220 persons invited to screening (42%) actually underwent colonoscopy. The median follow-up was 10 years, 91% had a good or very good bowel preparation, 97% achieved intubation of the cecum, and 30.7% had an adenoma detected. The risk of CRC was higher in the screened group for the first 5 years after colonoscopy (due to cancer diagnoses during the exams and heightened surveillance for pre-cancerous lesions, presumably), but was then less likely thereafter. In the intention-to-treat analysis, the incidence of CRC was significantly lower in the screened group (0.98% vs 1.20%; relative risk [RR] 0.82; 95% CI 0.70 - 0.93; number needed to invite [NNI] = 455 over 10 years). CRC mortality was not significantly lower in the screened group (0.28% vs 0.31%; RR 0.9; 0.64 - 1.16). There was no difference in all-cause mortality (11.03% vs 11.04%). The authors performed a separate per-protocol analysis to estimate the apparent benefits if everyone invited to colonoscopy had been screened, adjusting for baseline differences between those accepting the invitation and those who ignored it (important to at least partially adjust for the healthy volunteer bias). They estimate a lower incidence of CRC (0.84% vs 1.22%; RR 0.69; 0.55 - 0.83; number needed to screen [NNS] = 263) and a greater reduction in CRC mortality (0.15% vs 0.30%; RR 0.50; 0.27 - 0.77; NNS = 667). Complications were rare: 15 episodes of major bleeding (0.13%, 0 fatal) and no perforations.
Bottom line: In the first randomized trial of CRC screening using colonoscopy, a smaller than expected reduction in CRC incidence was seen in both the intention-to-treat (absolute risk reduction [ARR] = -0.22% over 10 years; NNI = 455) and adjusted per-protocol analyses (ARR = -0.38%; P < .05; NNS = 263). The same was true for reduction in CRC mortality in the intention-to-treat analysis (ARR = -0.03%; P = NS) and per-protocol analysis (ARR -0.15%; P < .05). The lower-than-expected mortality reduction may be explained in part by improvements in treatment and the modest duration of follow-up. The authors were careful to try to adjust for differences between invitees who accepted colonoscopy and those who did not (to avoid the healthy volunteer bias), although unmeasured confounding is still possible. Trials comparing fecal immunochemical test with colonoscopy are nearing their conclusion, and the results may add further clarity.
Bretthauer M, Loberg M, Wieszczy P, et al, for the NordICC Study Group. Effect of colonoscopy screening on risks of colorectal cancer and related death. N Engl J Med 2022;387(17):1547-1556

Here are the key results comparing USPSTF modeling and NordICC results:

	USPSTF Modeling	NordICC
CRC incidence	NNS =20	NNS = 263
CRC mortality	NNS = 39	NNS = 667

But what about comparisons of FIT with colonoscopy? We know that FIT is cheaper and results in fewer lifetime colonoscopies. It is also more acceptable, with higher rates of uptake in randomized trials. The next study looked at the yield of 10 years of biennial FIT testing in northern Italy. They found detection rates similar to those seen in the US for a single screening colonoscopy.

POEM #3: FIT has similar yield as colonoscopy for colorectal cancer and advanced adenoma

Clinical question: What is the yield of a screening program based on fecal immunochemical testing every 2 years for 10 years?
Study design: Cohort (prospective)
Funding source: Government
Setting: Population-based
Synopsis: The 2 most widely recommended strategies for CRC screening are FIT and colonoscopy. Several trials are currently underway to compare these approaches, with cancer-specific mortality as the primary outcome. Until then, we have to rely on observational studies and modeling to understand the benefit of each approach. Although colonoscopy is more sensitive than FIT, especially for the detection of advanced adenomas, what matters is performance over a long-term screening program, not one-time accuracy. This study reports the results of 5 rounds of biennial FIT in a screeening population aged 50 to 69 years in the Veneto region of northern Italy. Not surprisingly, the rate of detection of CRC was highest in the first round of screening when prevalent lesions were detected (3.3/1000 persons), declining in subsequent rounds and stabilizing after the third round (~1/1000 persons). Between rounds 3 and 6, the CRC detection rate declined slightly from 0.95 to 0.84 per 1000. A similar pattern was seen for advanced adenomas,

declining from 15.9 per 1000 persons to approximately 10 per 1000 persons in subsequent rounds. Over the 10-year study period, the cumulative rate of positive FIT results was 25% for men and 17.6% for women. The cumulative rate for advanced adenoma was 60 per 1000 persons, and for CRC was 8.5 per 1000 persons. These rates are similar to those seen in studies of colonoscopy in both Italy and the United States.
Bottom line: Over a 10-year period, the rates of detection of colorectal cancer (CRC) and advanced adenomas using fecal immunochemical testing (FIT) are similar to those seen in studies of screening colonoscopy. This is reassuring, but it does not prove that FIT reduces morbidity and mortality due to CRC as effectively as colonoscopy. Modeling concludes that a FIT-based screening program will result in half as many colonoscopies as a program based on colonoscopy, a significant reduction in cost, burden, and harm of screening. (LOE = 2b)
Zorzi M, Hassan C, Capodaglio G, et al. Long-term performance of colorectal cancer screening programmes based on the faecal immunochemical test. Gut 2018;67(12):2124-2130.

This next study is the first published study comparing colonoscopy with FIT in a randomized trial and reporting clinical outcomes. Uptake was better for FIT (40%) than for colonoscopy (21%). In the as randomized, intention to screen trial that takes the population perspective there was no difference between groups in CRC incidence or mortality. But…twice as many people in the FIT group got screened compared to those in the colonoscopy, due to greater uptake. When you compare the as screened results, then colonoscopy starts looking better:

As Screened Results	Colo 10 yr risk %	FIT 10 yr risk %	Non-participant 10 yr risk %	Colo vs non-participants RR (95% CI)	FIT vs non-participants RR (95% CI)
CRC mortality	0.03%	0.09%	0.32%	**0.10 (.02-.43)***	**0.28 (.15-.51)***
CRC incidence	0.87%	1.16%	1.27%	**0.68 (.48-.95)***	0.91 (.75-1.11)
All-cause mortality	4.21%	5.21%	9.43%	**0.47 (.39-.51)***	**0.55 (.51-.60)***

Note the much higher mortality in non-participants, mostly due to things other than CRC. This is the "healthy volunteer bias" in action, so the analysis should have adjusted for differences between adherent and non-adherent patients.

POEM #4: Randomized trial of colonoscopy vs FIT: Initial results (COLONPREV)

Background: Colonoscopy and the faecal immunochemical test are accepted strategies for colorectal cancer screening in the average-risk population (ie, people aged ≥50 years without personal or family history of colorectal cancer). In this trial, we aimed to compare whether invitation to screening with faecal immunochemical test was non-inferior to colonoscopy in a screening programme.
Methods: COLONPREV was a pragmatic, randomised, controlled, non-inferiority trial done at 15 tertiary hospitals across eight regions of Spain. Eligible participants were presumptively healthy and aged between 50 years and 69 years without a personal history of colorectal cancer, adenoma or inflammatory bowel disease, family history of hereditary or familial colorectal cancer (ie, two or more first-degree relatives with colorectal cancer or one diagnosed before age 60 years), severe comorbidities, or previous colectomy. Participants were randomly assigned (1:1) to one-time colonoscopy or biennial faecal immunochemical test before invitation to screening. The primary endpoint was colorectal cancer mortality at 10 years, assessed in the intention-to-screen population. An absolute difference of less than 0·16 percentage points was required to show non-inferiority. This trial was registered with ClinicalTrials.gov, NCT00906997.
Findings: Between June 1, 2009, and Dec 31, 2021, 57 404 individuals were randomly assigned to receive an invitation for colonoscopy (n=28 708) or the faecal immunochemical test (n=28 696). The intention-to-screen population consisted of 26 332 individuals in the colonoscopy group and 26 719 in the faecal immunochemical test group. In the intention-to-screen population, participation in any form of screening was 31·8% in the colonoscopy group and 39·9% in the faecal immunochemical test group (risk ratio [RR] 0·79 [95% CI 0·77 to 0·82]). Faecal immunochemical testing was non-inferior to colonoscopy with regard to the risk of colorectal cancer mortality at 10 years: the risk was 0·22% (55 deaths) in the colonoscopy group and 0·24% (60 deaths) in the faecal immunochemical test group (risk difference –0·02 [95% CI –0·10 to 0·06; RR 0·92 [95% CI 0·64 to 1·32]; p for non-inferiority=0·0005).
Interpretation Participation in screening was higher among individuals invited to faecal immunochemical test screening than colonoscopy screening. On the basis of participation observed in this study, a faecal immunochemical test-based programme was non-inferior to a colonoscopy-based programme for colorectal cancer-related mortality.
Funding: Fundación Científica de la Asociación Española contra el Cáncer and Instituto de Salud Carlos III.
Castells A, Quintero E, Bujanda L, et al. Effect of invitation to colonoscopy versus faecal immunochemical test screening on colorectal cancer mortality (COLONPREV): a pragmatic, randomised, controlled, non-inferiority trial. Lancet 2025; 405: 1231-9.

So FIT should be seen as a good option alongside colonoscopy.

For some reason, US patients are in many cases are getting colonoscopy too early or too often. Can't imagine why…

POEM #4: Screening colonoscopies are overused

Clinical question: What proportion of screening colonoscopies for cancer are not performed according to guideline parameters?
Study design: Systematic review

Setting: Various (meta-analysis)
Synopsis: These researchers searched 2 databases for English-language studies of screening colonoscopies for average-risk patients, identifying 6 studies with 242,756 screening colonoscopies. The studies defined colonoscopy overuse according to criteria from the US Preventive Services Task Force and the U.S. Multi-Society Task Force on Colorectal Cancer; that is, they are conducted in patients younger or older than the age range specified in national guidelines or at shorter intervals than recommended. The researchers followed PRISMA guidelines: 2 researchers selected articles for inclusion and 2 researchers independently abstracted data. These were all database studies. The studies reported 1 in 4 to 1 in 6 (17% to 25.7%) colonoscopies to be out of compliance with national guidelines.
Bottom line: From 17% to 25.7% of screening colonoscopies are performed too frequently or in patients who are too young or too old. In the United States alone, this rate translates into approximately 1 million colonoscopies performed each year outside of the parameters set by guidelines. As a reminder, screening via colonoscopy for colon cancer has never been shown to reduce overall mortality.
Fraiman J, Brownlee S, Stoto MA, Lin KW, Huffstetler AN. An estimate of the US rate of overuse of screening colonoscopy: a systematic review. J Gen Intern Med 2022 Feb 25:1–9.

The same group of researchers also looked at the harms. They did a systematic review looking at studies with adequate follow-up following screening colonoscopy.

POEM #5: Screening colonoscopy harms: 16 to 36 severe bleeds and 8 perforations/10,000 studies

Objective: This study aims to comprehensively assess the direct, severe harms of screening colonoscopy in the United States. Whereas other investigators have completed systematic reviews estimating the harms of all types of colonoscopy, this analysis focuses on screening colonoscopies that had adequate follow up to avoid undercounting delayed harms.
Data sources: PubMed and Embase were queried for relevant studies on screening colonoscopy harms published between January 1, 2002, and April 1, 2022.
Study selection: English-language studies of screening colonoscopy for average risk patients were included. Studies must have followed patients for adequate time post procedure, defined as 30 days after colonoscopy.
Main outcomes: The primary outcome was the number of severe bleeding events and gastrointestinal (GI) perforations within 30 days of screening colonoscopy.
Results: A total of 1951 studies were reviewed for inclusion; 94 were reviewed in full text. Of those reviewed in full, 6 studies, including a total of 467,139 colonoscopies, met our inclusion criteria and were included in our analysis of harms related to screening colonoscopies. The rate of severe bleeding ranged credibly from 16.4 to 36.18 per 10,000 colonoscopies; the rate of perforation ranged credibly from 7.62 to 8.50 per 10,000 colonoscopies.
Conclusions: This study is the first to estimate direct harms from screening colonoscopy, including harms that occur up to 30 days after the procedure. The risk of harm subsequent to screening colonoscopy is higher than previously reported and should be discussed with patients when engaging in shared decision making.
Huffstetler AN, Fraiman J, Brownlee S, Stoto MA, Lin KW. An Estimate of Severe Harms Due to Screening Colonoscopy: A Systematic Review, J Am Board Fam Med 2023 May 8;36(3):493-500. doi: 10.3122/jabfm.2022.220320R2. Epub 2023 May 11.

That amounts to 1 severe bleed for every 278 to 625 screening colonoscopies, and one perforation for every 1250 studies in the 30 days following the colonoscopy.

Breast Cancer Screening

USPSTF recommendation statement

- Screening mammography every other year in women aged 40-75 years
- No clinical breast exam, no recommendation for self-exam by women, no recommendation regarding women with dense breasts

American Cancer Society: From 40 to 44 consider annual mammogram; from 45 to 54 annual mammogram; from 55 until 10 years left annual or biennial mammograms
Canadian Task Force: provide women 40 to 75 with information about screening. Recommend not screening 40 to 49 and screen every 2 to 3 years from 50 to 74 years.
Norway: Mammogram every other year from 50 to 69 years
Netherlands: Mammogram every other year from 50 to 75 years

Mammography had been optional ages 40 to 49, but POEM #6 summarizes the new USPSTF recommendations that now recommend that all women start at age 40 years. So there must be some really important new data, right? The stated reason is a desire for equity, arguing that Black women have a higher incidence of and mortality due to breast cancer, and that starting at age 40 years would disproportionately benefit them. But current rates of screening mammography for Black women are actually higher than for white or Asian women (82% vs 76% vs 67%). Even more screening won't fix treatment disparities. Here are the data:

Table 2. Estimated Median Lifetime Benefits and Harms of Biennial Screening Mammography With Digital Breast Tomosynthesis for a Cohort of 1000 Women and a Cohort of 1000 Black Women by Starting Age of 40 vs 50 Years

Screening strategy (interval, start-stop ages in years)	Mammograms	Breast cancer deaths averted	Life-years gained	False-positive results	Overdiagnosis
All women (across 6 models)					
Biennial (40-74)	16 116	8.2	165.2	1376	14
Biennial (50-74)	11 208	6.7	120.8	873	12
Black women (across 4 models)					
Biennial (40-74)	15 801	10.7	228.9	1253	18
Biennial (50-74)	10 905	9.2	176.7	814	16

Starting age 40 vs 50 per 1000 women:

- Benefit: 1.5 more breast cancer diagnoses averted and 44 life years gained
- Harms: 500 more false positives, 2 more overdiagnosed and treated without benefit

POEM #6: USPSTF recommends mammography every other year for all women 40 to 74 years old

Clinical question: For which women is breast cancer screening recommended?
Study design: Practice guideline **Funding source**: Government
Setting: Various (guideline)
Synopsis: The 2016 United States Preventive Services Task Force (USPSTF) guideline recommended biennial mammography for women aged 50 to 74 years, and shared decision-making for women 40 to 49 years. (Full disclosure: I was one of the leads on this topic for the USPSTF at that time.) The statement emphasized the importance of risk assessment and noted that women with a first-degree relative with breast cancer should strongly consider beginning screening at age 40. The 2024 update to this USPSTF recommendation changes the age that screening is recommended for all women to 40 years. This is despite there being no new randomized trial evidence, and no substantive change in the estimated magnitude of benefits and harms based on modeling between 2016 and 2024. The stated reason is a greater desire for equity, arguing that Black women have a higher incidence of and mortality due to breast cancer, and that starting at age 40 years would disproportionately benefit them. Current rates of screening mammography for Black women are actually higher than for white women or Asian women (82% vs 76% vs 67%). The guideline provides a very helpful table of benefits and harms stratified by starting age (40 vs 50 years) and race (all women vs Black women only). For 2000 women of all races, starting at age 40 averts 3 deaths and adds 90 years of life for those women, while leading to 1000 more false positives and 4 additional overdiagnosed cancers. For 2000 Black women, starting at age 40 also averts 3 deaths and adds 105 years of life, while leading to 880 more false positives and 4 additional overdiagnosed cancers. An accompanying editorial argues that shared decision-making should remain a consideration for average-risk women in their 40s based on the substantial harms of screening. Overdiagnosis, perhaps the most substantial harm, leads to physical and emotional harm without any possibility of benefit. The guideline found insufficient evidence to recommend for or against screening after age 74 years or screening using supplemental technologies such as ultrasound and magnetic resonance imaging.
Bottom line: The USPSTF now recommends that all women receive a screening mammogram every other year from age 40 to 74 years. For 2000 women screened starting at age 40 instead of 50, 3 more women avoid death and gain 90 years of life, at a cost of 1000 more false positives and 4 additional overdiagnosed cancers. Countries also recommending screening starting at age 40 years include Sweden, Japan, and Iceland. (LOE = 1a)
US Preventive Services Task Force; Nicholson WK, Silverstein M, et al. Screening for breast cancer: US Preventive Services Task Force recommendation statement. JAMA 2024;331(22):1918-1930.

The next 2 POEMs address the role of supplemental imaging. The first finds preliminary evidence that for women with very dense breasts (grade 4/4) supplemental MRI can reduce interval invasive cancers when mammography is done every 2 years as is the recommendation from every group in the world other than American radiologists. The second finds no benefit to supplemental ultrasound.

POEM #7: Supplemental MRI screening in women with very dense breasts reduces interval cancer rate but may cause overdiagnosis (DENSE)

Clinical question: Does supplemental magnetic resonance imaging screening for women with very dense breasts reduce the number of interval cancers?
Study design: Randomized controlled trial (nonblinded)
Setting: Population-based
Synopsis: Almost all guidelines recommend mammography every 2 years, typically in women aged 50 to 69 or 75 years. (The sole exception is the US American College of Radiology, which continues to recommend annual screening. Go figure.) In this Dutch study, women undergoing routine digital mammography who were identified as having very dense breast tissue (grade 4/4) and who had a

normal digital mammogram result were randomized in a 1:4 ratio to receive supplemental MRI screening or usual care. After randomization, the women in the MRI group were notified and invited to participate. Obtaining consent after randomization is known as a Zelen design, and is thought to reduce protocol violations and anxiety in the women not randomized to MRI. Women with a Breast Imaging Reporting and Data System (BI-RADS) MRI score of 4 or 5 were recalled for further evaluation including biopsy. Women with a BI-RADS score of 3 had a second reading of the MRI and if the second reading was also 3, they had a follow-up MRI in 6 months. The primary outcome was the likelihood of interval cancer, defined as all cancers detected in the 24 months following a negative index digital or MRI mammogram and before the next scheduled mammogram (or within 24 months if aging out of the cohort). A total of 8061 women were randomized to receive supplemental MRI screening; 4783 (59%) agreed to the screening. The comparison group had 32,312 women. Of the 4783 women who underwent supplemental MRI screening, 79 (1.65%) had breast cancer detected on MRI. In the intention-to-screen analysis that included all 8061 women randomized to MRI, the rate of interval cancers was lower than in the usual care group (2.5 vs 5.0 per 1000 women). This is the appropriate comparison, since in other mammography trials women who ignore the invitation to screen had worse health outcomes than those who chose to volunteer. Among women randomized to MRI, the rate of interval cancers was 0.8 per 1000 women in those who volunteered and 5.0 per 1000 women (nearly identical to the control group rate of 4.9/1000) in those who did not. With regard to harms, for women undergoing supplemental MRI screening, 9.5% were recalled and 6.3% of all women had a biopsy. The false positive rate was 8.0% among women undergoing supplemental MRI. Of the 79 cancers detected in MRI group, approximately 80% were invasive and the remainder were ductal carcinoma in-situ. The characteristics of the interval cancers did not differ significantly between groups. At the second round of screening, the rate of invasive cancers was lower in the MRI group than in the digital mammography–only group (2.0 vs 7.0 per 1000) and they were more likely to be stage 0 or 1 cancers, suggesting that MRI advanced the time of detection. The study was not powered to detect a reduction in mortality.
Bottom line: Supplemental magnetic resonance imaging (MRI) screening for women with very dense breasts, compared with mammography alone every 2 years, significantly reduces the likelihood of an interval cancer, from 5.0/1000 to 2.5/1000 in the intention-to-treat population and to 0.8/1000 in the per-protocol population. However, false positive results were common, and there were more overall cancers and more early-stage cancers detected in the MRI group, raising the concern that many of these may have been present but growing slowly and indolently (so-called overdiagnosed cancers). Subsequent follow-up will hopefully determine whether mortality and not just incidence is affected.
Bakker MF, de Lange SV, Pijnappel RM, et al, for the DENSE Trial Study Group. Supplemental MRI screening for women with extremely dense breast tissue. N Engl J Med 2019;381(22):2091-2102.

POEM #8: Adding ultrasound to mammography increases false-positive findings without an increase in cancer detection

Clinical question: Does the addition of screening ultrasound add benefit or harm to screening mammography alone?
Study design: Cohort (retrospective)
Setting: Outpatient (any)
Synopsis: These researchers compared the results from 6081 women who were screened for breast cancer with mammography and ultrasound with 30,062 screening mammograms from 15,176 women drawn from 13 years of data from 2 breast cancer surveillance registries in the United States. Most (74.3%) of the ultrasound screens were performed in women with dense breasts, and, as compared with the mammography-alone group, were more likely to be at higher risk of breast cancer or to be younger than 50 years. Despite these differences, the cancer detection rate was similar across groups (5.4 vs 5.5 per 1000 screens), as was the development of cancer between screenings (interval cancer rate). However, the rate of unnecessary biopsies was more than twice as high for the combination screening (52.0 vs 22.2 per 1000 screens), as were calls for rescreening at shorter-than-normally-recommended intervals (relative risk = 3.10; 95% CI 2.6 - 3.7).
Bottom line: Adding ultrasound to screening mammography in women younger than 50 years at low, intermediate, or high breast cancer risk is not associated with an increase in breast cancer detection. It is associated, however, with increased unnecessary biopsy recommendations and results in more frequent follow-up.
Lee JM, Arao RF, Sprague BL, et al. Performance of screening ultrasonography as an adjunct to screening mammography in women across the spectrum of breast cancer risk. JAMA Intern Med 2019;179(5):658-667.

Lung Cancer Screening

USPSTF recommendation statement

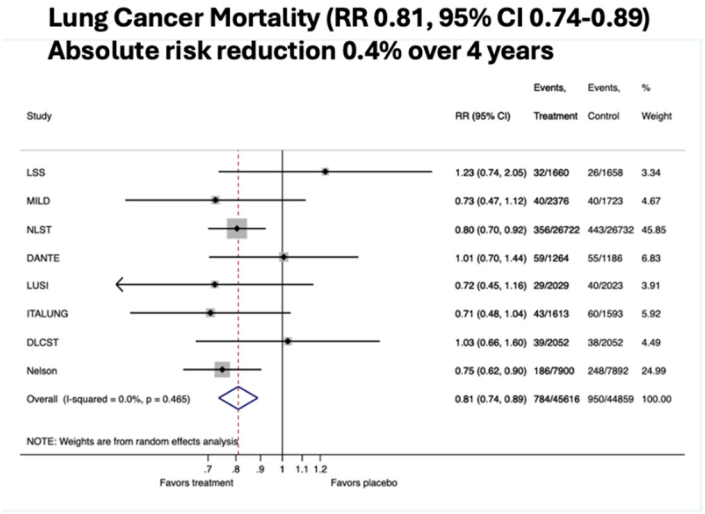
Who: Adults aged 50 to 80 years who have a 20 pack-year history and currently smoke or who quit in the last 15 years.
What: Low dose CT scan (radiation about 1/3 of annual background radiation)
How often: Annually
How long: ???

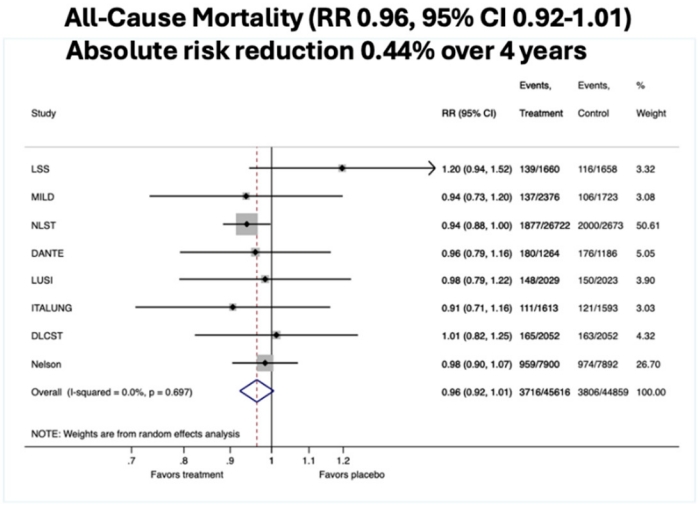
So how much benefit is there? It turns out that the only test for which there is evidence of reduced all-cause mortality from a single study was the National Lung Screening Trial funded by NIH. Here is a meta-analysis summarizing all 8 randomized trials to date.

POEM #9: Screening smokers for lung cancer with low-dose CT decreases lung cancer mortality

Clinical question: Does low-dose computerized tomography screening for lung cancer prevent mortality in smokers?

Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: The authors of the current study used references from a systematic review (published in 2019) and conducted a supplemental search of PubMed. They only included randomized trials at low risk of bias (based on the Cochrane Risk of Bias tool). These authors identified the same 9 randomized trials, but one was deemed to be at high risk of bias (based on the Cochrane Risk of Bias tool), leaving 8 studies with 90,475 participants. The 8 studies enrolled persons with 20 to 30 or more pack-years of smoking and who ranged from 45 to 75 years of age. The median follow-up ranged from 5.2 years to 10 years and the lung cancer mortality varied from 1.6% to 4.6%. After pooling the results, persons screened with low-dose computed tomography were less likely to die from lung cancer (relative risk [RR] 0.81; 95% CI 0.74 - 0.89; number needed to treat = 251; 173 - 454). Although all-cause mortality was slightly lower in the screened group, this was not statistically significant (RR 0.96; 0.92 - 1.01). The mortality data were fairly homogeneous across studies. Other than identifying an overdiagnosis rate of approximately 20%, the authors don't report on the harms of screening.
Bottom line: High-quality screening trials show that low-dose computerized tomography decreased lung cancer mortality in smokers.
Ebell MH, Bentivegna M, Hulme C. Cancer-specific mortality, all-cause mortality, and overdiagnosis in lung cancer screening trials: a meta-analysis. Ann Fam Med 2020;18(6):545-552.





NNS to prevent 1 lung cancer death = 251

NNS to prevent 1 death overall =225

POEM #10: Volume-based low-dose CT screening reduces lung cancer–specific mortality (NELSON)

Clinical question: Does volume-based low-dose computed tomographic screening reduce lung cancer–specific mortality?
Study design: Randomized controlled trial (nonblinded)
Setting: Population-based
Synopsis: To date, the National Lung Screening Trial is the only individual study (out of several to date) to demonstrate reduced lung cancer–specific (and all-cause) mortality by screening high-risk persons with low-dose computed tomography (CT). This Dutch study used a protocol based on the volume of nodules and doubling time to identify which patients needed additional imaging or referral for biopsy. They identified 13,195 men and 2594 women, aged 50 to 74 years, who had smoked 15 cigarettes a day for at least 25 years or 10 cigarettes a day for at least 30 years, and were either current smokers or had quit within the last 10 years. Participants were randomized to receive screening with low-dose CT at baseline, 1 year later, 3 years later, and 5.5 years later, or usual care. The cause of death was determined from national registries and, if necessary, by review of a cause of death committee. The mean age of participants was 58 years, the median pack-years of smoking was 38 years, and 55% were current smokers. After a mean 8.8 years of follow-up, the primary outcome of lung cancer mortality for men and women (based on data from the Appendix) was significantly lower in the screened group (relative risk [RR] 0.75; 0.62 - 0.90). For men, the cumulative rate ratio was 0.76 (0.61 - 0.95); for women, it was 0.67 (0.38 - 1.14). The absolute risk reduction was 0.8% over the study period, for a number needed to screen to prevent 1 lung cancer death of 127. There was no difference in all-cause mortality, but the study was not powered for this outcome. Overall, only 2.1% of test results were classified as positive and required evaluation for biopsy.
Bottom line: The results of this trial are consistent with the results from the National Lung Screening Trial, with a reduction in lung cancer–specific mortality that was clinically and statistically significant.
de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung cancer mortality with volume CT screening in a randomized trial. N Engl J Med 2020;382(6):503-513.

Blood tests for cancer

POEM #11: Multicancer early detection numbers needed to screen: 1000 to detect one stage 1 or 2 cancer, 530 to detect any cancer (SPOT-MAS)

Clinical question: How accurate is a novel multicancer early detection test in asymptomatic adults with no history of cancer?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: Multicancer early detection (MCED) tests are being promoted as a “liquid biopsy” to simultaneously screen for dozens of different cancers. They couple detection of circulating fragments of tumor DNA with sophisticated artificial intelligence models. The current study evaluated such a test called SPOT-MAS from a Singaporean company in a population of 9057 asymptomatic Vietnamese

adults 40 years and older without a history of cancer or known symptoms of cancer. The median age was 50 years and 55% were women. Any positive test results were followed by an extensive diagnostic evaluation while patients who tested negative were followed up for one year to identify any subsequent cancer diagnoses unrelated to the MCED test during that period. This is similar to a study of the Galleri MCED test published in 2023, though in that study patients were at higher risk, including 24% with a previous history of successfully treated cancer. The results of both studies are summarized in the following table.

	SPOT-MAS (n = 9024)	**Galleri (n = 6662)**
Positive test results	43 (0.48%)	92 (1.38%)
New cancers	17 (0.19%)	29 (0.44%)
Stage 1 or 2	9 (0.1%)	14 (0.21%)
Stage 3	3 (0.03%)	9 (0.14%)
Stage 4	5 (0.05%)	6 (0.09%)
Sensitivity	70.8%	28.9%
Specificity	99.7%	99.1%
Positive predictive value	39.5%	38%
Negative predictive value	99.92%	98.6%

SPOT-MAS (n = 9024) Galleri (n = 6662) Positive test results 43 (0.48%) 92 (1.38%) New cancers 17(0.19%) 29 (0.44%) Stage 1 or 2 9 (0.1%) 14 (0.21%) Stage 3 3 (0.03%) 9 (0.14%) Stage 4 5 (0.05%) 6 (0.09%) Sensitivity 70.8% 28.9% Specificity 99.7%99.1% Positive predictive value 39.5% 38% Negative predictive value 99.92% 98.6% The tests were successfully designed to avoid a large number of false positives, with specificities higher than 99% for both tests. Approximately one-third of patients in both studies with a positive test result had a cancer diagnosis confirmed. About half of patients with cancer in both studies had a stage 1 or 2 cancer, likely to be amenable to treatment; in the Galleri study, 7 of 14 stage 1 or 2cancers were follicular lymphomas. Also, 11 of 17 cancers detected by SPOT-MAS were cancers for which screening was recommended by the U.S. Preventive Services Task Force. The sensitivity is probably overestimated, as the patients with a negative SPOT-MAS test result did not undergo a systematic evaluation for cancer, with the researchers relying on self-report.
Bottom line: The number needed to screen to detect a stage 1 or 2 cancer was 1000 for the SPOT-MAS test in an average risk population. If its cost is similar to that of Galleri ($950), that is approximately US$1 million to detect a single stage 1 or 2 cancer (not including the cost and potential harms of the diagnostic evaluations). Large scale trials that are evaluating the impact on mortality and other important clinical outcomes are underway. Until then, these tests should not be recommended to our patients.
Nguyen LHD, Nguyen THH, Le VH, et al. Prospective validation study: a noninvasive circulating tumor DNA-based assay for simultaneous early detection of multiple cancers in asymptomatic adults. BMC Med 2025;23(1):90

POEM #12: Cell-free DNA blood test 83% sensitive for colorectal cancer, 13% sensitive for advancedadenoma; mortality data lacking (ECLIPSE)

Clinical question: How accurate is a cell-free DNA blood test compared with colonoscopy for colorectal cancer or advanced adenoma screening?
Study design: Diagnostic test evaluation
Setting: Outpatient (specialty)
Synopsis: This study evaluates a new screening test for colorectal cancer that tries to detect cell-free DNA in blood samples. These industry-funded researchers initially enrolled 22,877 participants who were undergoing a screening colonoscopy, of whom 65 had colorectal cancer. Participants were 45 to 84 years old and at average risk for colorectal cancer. The authors took a random sample of 10,258 participants without cancer and added back the 65 with cancer to create an enriched final study population. Doing this artificially increased the predictive value by increasing the prevalence of cancer in the study sample from 0.28% to 0.82%. Of those10,258, 2397 were excluded (mostly due to no or incomplete colonoscopy, no blood test, or invalid blood test result) leaving a final study population of 7861. The mean age of participants in the final population was 60 years, 54% were women, and 22% were non-White. The sensitivity of the test for colorectal cancer was83%, and the sensitivity for stage I, II or III colorectal cancer was 87%. However, the sensitivity for advanced adenomas was only 13%. Specificity for an outcome other than cancer or advanced adenoma was 90%. The authors estimate that based on an average-risk population of 100,000 persons (they use 0.42% prevalence),slightly more than 11,000 will have an abnormal test result requiring colonoscopy, of whom 3.2% will have cancer and 12.9% an advanced adenoma.
Bottom line: A blood-based test for colorectal cancer had reasonable sensitivity for cancer (83%) and good specificity, but poor sensitivity for advanced adenomas. The sensitivity for advanced adenoma of 13% compares with 23% for the fecal immunochemical test (FIT) and 43% for a fecal DNA plus FIT as described in a separate study in the same issue of the journal. Ideally, a randomized trial of sufficient size and duration could determine which test (colonoscopy, FIT, fecal DNA plus FIT, or this blood test) provides the best balance among mortality reduction, harms, and cost. In theory, modeling could help answer this, but the large discrepancy between U.S. Preventive Services Task Force modeling studies and the results of the recent NordICC randomized trial make some of us question its validity. Overall, this blood test is inferior in terms of sensitivity to the fecal DNA plus FIT (93.9%) and FIT alone is much cheaper than both. It remains uncertain which test provides the best mortality reduction over a 20- or 30-year program of screening.
Chung DC, Gray DM, Singh H, et al. A cell-free DNA blood-based test for colorectal cancer screening. NEJM 2024;390(11):973-983.

POEM #13: Recommendations for care outpace the time available for a typical primary care practice

Clinical question: How much time does it take for a primary care clinician to implement applicable guidelines for prevention and care in a typical practice?
Study design: Other

Setting: Other
Synopsis: These authors conducted a theoretical modeling study to estimate the time needed to provide all the preventive care, chronic care, and acute care according to current guidelines. To estimate the time burden on a typical primary care practice, they created 1000 hypothetical primary care panels of 2500 patients. They identified all the Grade A and Grade B preventive care guidelines for adults from the United States Preventive Services Task Force and the Advisory Committee on Immunization Practices of the Centers for Disease Control (N = 48). The authors picked guidelines for the top 10 chronic illnesses and calculated the average number and length of visits for acute illness among adults. They estimated the time with and without team-based care. The complete basket of services was estimated to require 26.7 hours per day, which includes 3.2 hours each day for documentation and inbox management, 14.1 hours for preventive care, 7.2 hours for chronic disease care, and 3.2 hours a day for acute care. Panel size affects work: Decreasing to a panel size of 1500 patients decreases physician time by 10.7 hours and increasing to 3000 patients increases time by 5.3 hours. Estimates for practices using high-functioning teams are lower: 9.3 hours per day of clinician time, which includes 2.6 hours per day for and inbox management. These estimates don't likely apply to countries with healthcare systems that aren't driven by insurance companies and their documentation requirements.
Bottom line: Well, it's good to know that a typical primary care clinician with a typical patient panel on a typical day can provide all necessary preventive care and acute and chronic illness care. Yeah, I'm kidding: The true estimate, if all boxes were ticked and all problems were completely addressed for all patients, is 26.7 hours a day,I ncluding 3.2 hours each day to care for and feed the electronic medical record monster. Using team-based care helps, but at an average 9.3 hours per day, don't expect to eat lunch or get home on time for dinner. Some pundits have asked guideline developers to consider the "time needed to treat" when formulating their advice.
Porter J, Boyd C, Skandari MR, Laiteerapong N. Revisiting the time needed to provide adult primary care. J Gen Intern Med 2023;38(1):147-155.

POEM #14: 0 cases of invasive cervical cancer in women who received at least 1 dose of bivalent HPV vaccine at 12 or 13 years of age

Clinical question: How effective is the bivalent human papilloma virus vaccine in preventing invasive cervical cancer?
Study design: Cohort (prospective)
Setting: Population-based
Synopsis: These researchers linked several information sources from Scotland, including the National Health Service Scotland, the Scottish Cervical Cancer Call Recall System, and the Scottish Cancer Registry. The authors used postal codes to determine the Scottish Index of Multiple Deprivation, which includes income, employment, education, health, access to services, crime, and housing data. From these sources, they determined the number of human papilloma virus (HPV)vaccine doses, the age of administration, and the rates of cervical carcinoma. They included women born between 1988 and 1996 and used July 2020 cancer data. Ultimately, the researchers analyzed data on 447,845 women, 239 of whom had developed invasive cervical cancer. They identified no cases of invasive cervical cancer in adults who received any doses of HPV vaccine when they were 12 to 13 years of age. Very few 12- to 13-year-old girls (411) were partially immunized. Additionally, partial immunization in children 14 years or older was ineffective. The unvaccinated women were primarily older women who did not receive catch-up immunizations. Although the cancer incidence was highest among women with the greatest deprivation index, the vaccinated women in this group had the greatest reduction in cervical cancer incidence. The following table summarizes the number of cases of invasive cervical cancer, the incidence rate per 100,000women, and the vaccine effectiveness (adjusted for deprivation index).

Group	Number of cancers	Cancer incidence (95% CI)	Vaccine effectiveness (95% CI)
Unvaccinated	210	8.4 (7.2 - 9.6)	—
Partial vaccination at 12-13 y	0	0.0 (0.0 - 199.6)	Too few to calculate
Complete vaccination at 12-13 y	0	0.0 (0.0 - 2.7)	100 (66.9 - 100)
Partial vaccination at 14+ y	8	6.5 (2.6 t - 13.6)	40.0 (-22.8 to 70.7)
Complete vaccination at 14+ y	21	2.7 (1.7 - 4.2)	73.8 (58.9 - 83.4)

Bottom line: The data are fairly convincing that the HPV vaccine is effective in preventing invasive cervical cancer, especially when given to 12- to 13-year-olds. Partial immunization in older children was potentially ineffective. This study evaluated the real-world effectiveness of the bivalent vaccine that has largely been replaced by nona-valent HPV vaccines. Finally, the vaccine had its greatest effectiveness among women living in the lowest socioeconomic strata.
Palmer TJ, Kavanagh K, Cuschieri K, et al. Invasive cervical cancer incidence following bivalent human papillomavirus vaccination: a population-based observational study of age at immunization, dose, and deprivation. J Natl Cancer Inst 2024 Jan 22:djad263. Epub ahead of print.

Bottom-Lines

1. Screen for colorectal cancer, although the benefits may not be as dramatic as previously expected. Use colonoscopy every 10 years or FIT every 1 to 2 years. They are probably pretty similar in effectiveness.
2. Screening for colorectal cancer starting at age 45, or breast cancer starting at age 40, both have small benefits and harms.
3. Adding MRI may be beneficial for women with dense breasts, but ultrasound does not seem to add anything.
4. Lung cancer screening has the most favorable NNT of any major cancer screening test.

Diabetes Update Gary Ferenchick MD

Objectives, understand:

- Decoupling A1c from Outcomes (Targeting Risk, Not Just Glucose)
- Obesity & T2D
- Diabetes and the pivotal role of GLP-1 receptor agonists.
  - This data is rapidly evolving

Disease vs Patient-oriented outcomes in diabetes | A brief history

In any condition what actually happens to patients (death, disease, discomfort, disability and dissatisfaction) is more important than what happens to surrogate outcomes. A case in point are several examples from the annals of research in DM2.

First is the brief story on rosiglitazone.

- A RCT of 533 patients randomized to rosiglitazone 2 or 4 mg daily (N=335; mean age 61; Average A1c 8.9%) or placebo (N=158; mean age 59; Average A1c 9.0%) demonstrated a 1.2 - 1.5% decrease in A1c In addition to other "benefits" including insulin resistance and improved beta cell function, etc). (*Rosiglitazone monotherapy is effective in patients with type 2 diabetes. J Clin Endocrinol Metab. 2001 Jan;86(1):280-8*).
- Using a "glucocentric" metric this was a good result
- But not so fast, in a meta-analysis of 42 RCTs the OR for MI or CV death was increased by 43 - 64% in patients on rosiglitazone. (*Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. N Engl J Med 2007; 356:2457-2471*)

“In 2008, the FDA issued guidance for industry to perform cardiovascular outcomes trials for all new medications for the treatment of type 2 diabetes amid concerns of increased cardiovascular risk. Previously approved diabetes medications were not subject to the guidance." (ADA SOC 2024)

Second is the ACCORD Trial

- Where the more intensive glycemic control (6.4% vs 7.5% a “positive result”) was associated with a 22% increase in mortality (a bad result).

Both of these examples demonstrated that the "positive" disease-oriented outcome were associated with a negative patient oriented outcome.

This has ultimately led to a substantial shift in thinking about the pharmacomanagement of T2D in the past several years, away from a strict focus on glycemic control (disease-oriented) to matching patient comorbidities with specific pharmacotherapies (mostly GLP-1 agonists and/or SGLT2 inhibitors) irrespective of the need for additional glucose lowering

Although in 2024 the ADA still endorses some focus on glycemic targets, my reading of these recommendation (in total) demonstrates a shift away from targeting the A1c and toward matching therapy to patient characteristics (irrespective (ish) of A1c). They continue to offer guidance on who should be considered for more vs less tight control of A1c.

1. Crucial role of body weight loss in managing T2D

Background: Bodyweight loss is associated with type 2 diabetes remission; however, the quantitative relationship between the degree of bodyweight loss and the likelihood of remission, after controlling for confounding factors, remains unknown. We aimed to analyse the relationship between the degree of bodyweight loss and diabetes remission after controlling for various confounding factors, and to provide estimates for the effect sizes of these factors on diabetes remission.

Methods: This systematic review and meta-regression analysis followed Cochrane and PRISMA guidelines to systematically review, synthesise, and report global evidence from randomised controlled trials done in individuals with type 2 diabetes and overweight or obesity. The outcome was the proportion of participants with complete diabetes remission (HbA1c <6·0% [42 mmol/mol] or fasting plasma glucose [FPG] <100 mg/dL [5·6 mmol/L], or both, with no use of glucose-lowering drugs) or partial diabetes remission (HbA1c <6·5% [48 mmol/mol] or FPG <126 mg/dL [7·0 mmol/L], or both, with no use of glucose-lowering drugs) at least 1 year after a bodyweight loss intervention. We searched PubMed, Embase, and trial registries from database inception up to July 30, 2024. Data were extracted from published reports. Meta-analyses and meta-regressions were performed to analyse the data. The study protocol is registered with PROSPERO (CRD42024497878).
Findings: We identified 22 relevant publications, encompassing 29 outcome measures of complete diabetes remission and 33 outcome measures of partial remission. The pooled mean proportion of participants with complete remission 1 year after the intervention was 0·7% (95% CI 0·1–4·6) in those with bodyweight loss less than 10%, 49·6% (40·4–58·9) in those with bodyweight loss of 20–29%, and 79·1% (68·6–88·1) in those with bodyweight loss of 30% or greater; no studies reported on complete remission with 10–19% bodyweight loss. The pooled mean proportion of participants with partial remission 1 year after the intervention was 5·4% (95% CI 2·9–8·4) in those with bodyweight loss less than 10%, 48·4% (36·1–60·8) in those with 10–19% bodyweight loss, 69·3% (55·8–81·3) in those with bodyweight loss of 20–29%, and 89·5% (80·0–96·6) in those with bodyweight loss of 30% or greater. There was a strong positive association between bodyweight loss and remission. For every 1 percentage point decrease in bodyweight, the probability of reaching complete remission increased by 2·17 percentage points (95% CI 1·94–2·40) and the probability of reaching partial remission increased by 2·74 percentage points (2·48–3·00). No significant or appreciable associations were observed between age, sex, race, diabetes duration, baseline BMI, HbA1c, insulin use, or type of bodyweight loss intervention and remission. Overall, data were derived from randomised controlled trials with a low risk of bias in all quality domains.
Interpretation:A robust dose–response relationship between bodyweight loss and diabetes remission was observed, independent of age, diabetes duration, HbA1c, BMI, and type of intervention. These findings highlight the crucial role of bodyweight loss in managing type 2 diabetes and reducing the risk of diabetes-related complications.
Impact of bodyweight loss on type 2 diabetes remission: a systematic review and meta-regression analysis of randomised controlled trials. Kanbour, Sarah et al.The Lancet Diabetes & Endocrinology, 2025 Volume 13, Issue 4, 294 - 306

- Weight loss is the primary driver of remission—not age, race, baseline A1c, diabetes duration, insulin use, or intervention type.
- Therefore, prioritizing meaningful weight loss as a therapeutic goal

Depending on the study, semaglutide and tirzepatide use after about 1 year are associated with 10 – 15% (may be more) weight loss with improved metabolic parameters among obese patients with T2D.

2. Tirzepatide or semaglutide assoc with 15 – 20% weight loss

Background: Tirzepatide and semaglutide are highly effective medications for obesity management. The efficacy and safety of tirzepatide as compared with semaglutide in adults with obesity but without type 2 diabetes is unknown.
Methods: In this phase 3b, open-label, controlled trial, adult participants with obesity but without type 2 diabetes were randomly assigned in a 1:1 ratio to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or the maximum tolerated dose of semaglutide (1.7 mg or 2.4 mg) subcutaneously once weekly for 72 weeks. The primary end point was the percent change in weight from baseline to week 72. Key secondary end points included weight reductions of at least 10%, 15%, 20%, and 25% and a change in waist circumference from baseline to week 72.
Results: A total of 751 participants underwent randomization. The least-squares mean percent change in weight at week 72 was −20.2% (95% confidence interval [CI], −21.4 to −19.1) with tirzepatide and −13.7% (95% CI, −14.9 to −12.6) with semaglutide (P<0.001). The least-squares mean change in waist circumference was −18.4 cm (95% CI, −19.6 to −17.2) with tirzepatide and −13.0 cm (95% CI, −14.3 to −11.7) with semaglutide (P<0.001). Participants in the tirzepatide group were more likely than those in the semaglutide group to have weight reductions of at least 10%, 15%, 20%, and 25%. The most common adverse events in both treatment groups were gastrointestinal, and most were mild to moderate in severity and occurred primarily during dose escalation.
Conclusions: Among participants with obesity but without diabetes, treatment with tirzepatide was superior to treatment with semaglutide with respect to reduction in body weight and waist circumference at week 72.
Tirzepatide as compared with semaglutide for the treatment of obesity. N Engl J Med. 2025;390(22):2045–2056.

3. Tirzepatide for diabetes prevention

Background: Obesity is a chronic disease and causal precursor to myriad other conditions, including type 2 diabetes. In an earlier analysis of the SURMOUNT-1 trial, tirzepatide was shown to provide substantial and sustained reductions in body weight in persons with obesity over a 72-week period. Here, we report the 3-year safety outcomes with tirzepatide and its efficacy in reducing weight and delaying progression to type 2 diabetes in persons with both obesity and prediabetes.
Methods: We performed a phase 3, double-blind, randomized, controlled trial in which 2539 participants with obesity, of whom 1032 also had prediabetes, were assigned in a 1:1:1:1 ratio to receive tirzepatide at a once-weekly dose of 5 mg, 10 mg, or 15 mg or placebo. The current analysis involved the participants with both obesity and prediabetes, who received their assigned dose of tirzepatide or placebo for a total of 176 weeks, followed by a 17-week off-treatment period. The three key secondary end points, which were controlled for type I error, were the percent change in body weight from baseline to week 176 and onset of type 2 diabetes during the 176-week and 193-week periods.
Results: At 176 weeks, the mean percent change in body weight among the participants who received tirzepatide was -12.3% with the 5-mg dose, -18.7% with the 10-mg dose, and -19.7% with the 15-mg dose, as compared with -1.3% among those who received placebo

(P<0.001 for all comparisons with placebo). Fewer participants received a diagnosis of type 2 diabetes in the tirzepatide groups than in the placebo group (1.3% vs. 13.3%; hazard ratio, 0.07; 95% confidence interval [CI], 0.0 to 0.1; P<0.001). After 17 weeks off treatment or placebo, 2.4% of the participants who received tirzepatide and 13.7% of those who received placebo had type 2 diabetes (hazard ratio, 0.12; 95% CI, 0.1 to 0.2; P<0.001). Other than coronavirus disease 2019, the most common adverse events were gastrointestinal, most of which were mild to moderate in severity and occurred primarily during the dose-escalation period in the first 20 weeks of the trial. No new safety signals were identified.
Conclusions: Three years of treatment with tirzepatide in persons with obesity and prediabetes resulted in substantial and sustained weight reduction and a markedly lower risk of progression to type 2 diabetes than that with placebo. (Funded by Eli Lilly; SURMOUNT-1 ClinicalTrials.gov number, NCT04184622.).
Tirzepatide for Obesity Treatment and Diabetes Prevention. *N Engl J Med. 2025 Mar 6;392(10):958-971.*

"The prevalence of overweight or obesity among adults diagnosed with type 2 diabetes exceeds 85%.Bodyweight loss is associated with remission of type 2 diabetes, which is currently defined as HbA1c less than 6·5% or fasting plasma glucose (FPG) less than 126 mg/dL, or both, measured at least 3 months after cessation of glucose-lowering pharmacotherapy" (The Lancet Diabetes & Endocrinology, 2025 Volume 13, Issue 4, 294 - 306).
GLP-1 receptor agonists and combined GIP/GLP-1 agonists induce substantial weight loss and significantly reduce the incidence of type 2 diabetes in high-risk individuals. However, if their benefits were limited only to diabetes prevention—without impacting the end-organ complications associated with diabetes—their role in chronic disease management, though meaningful, would be less compelling. In my view, the most important attribute of these drug classes is their demonstrated effect on disease-oriented outcomes, such as cardiovascular, renal, and hepatic health.

4. GLP-1 agonists and ASCVD Outcomes

GLP1 Agonists & ASCVD Outcomes						
Drug	**Duration**	**Δ MACE**	**Δ CHF endpoints**	**Δ Mortality**	**Δ Hypoglycemia**	**Δ A1c**
Liraglutide (NEJM 2016)	3.8	1.9%	NS	1.4%	0.9%	0.4%
Semaglutide | T2D (NEJM 2016)	2.1	3.2%	NS	2.2%	1.1%	~1.4%
Albiglutide (Lancet 2018)	1.5	2.0%	NS	NS	0	1.0%
Exenatide (NEJM 2017)	3.2	NS	NS	NS	0.4%	0.53%
Dulaglatide (Lancet 2019)	5.4	1.4%	NS	NS	0.2%	0.61%
Oral semaglutide (NEJM 2019)	1.3	NS	NS	1.4%	0.6%	0.7%
Lixisenatide (NEJM 2015)	2.1	NS	NS	NS	1.4%	0.27%

5. Oral semaglutide and ASCVD

Background: The cardiovascular safety of oral semaglutide, a glucagon-like peptide 1 receptor agonist, has been established in persons with type 2 diabetes and high cardiovascular risk. An assessment of the cardiovascular efficacy of oral semaglutide in persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both is needed.
Methods: In this double-blind, placebo-controlled, event-driven, superiority trial, we randomly assigned participants who were 50 years of age or older, had type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0%, and had known atherosclerotic cardiovascular disease, chronic kidney disease, or both to receive either once-daily oral semaglutide (maximal dose, 14 mg) or placebo, in addition to standard care. The primary outcome was major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), assessed in a time-to-first-event analysis. The confirmatory secondary outcomes included major kidney disease events (a five-point composite outcome).
Results: Among the 9650 participants who had undergone randomization, the mean (±SD) follow-up was 47.5±10.9 months, and the median follow-up was 49.5 months. A primary-outcome event occurred in 579 of the 4825 participants (12.0%; incidence, 3.1 events per 100 person-years) in the oral semaglutide group, as compared with 668 of the 4825 participants (13.8%; incidence, 3.7 events per 100 person-years) in the placebo group (hazard ratio, 0.86; 95% confidence interval, 0.77 to 0.96; P = 0.006). The results for the confirmatory secondary outcomes did not differ significantly between the two groups. The incidence of serious adverse events was

47.9% in the oral semaglutide group and 50.3% in the placebo group; the incidence of gastrointestinal disorders was 5.0% and 4.4%, respectively.
Conclusions: Among persons with type 2 diabetes and atherosclerotic cardiovascular disease, chronic kidney disease, or both, the use of oral semaglutide was associated with a significantly lower risk of major adverse cardiovascular events than placebo, without an increase in the incidence of serious adverse events
SOUL Study Group. Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes. NEJM 2025;392(20):2001-2012.

6. Semagludite & renal outcomes

Background: Patients with type 2 diabetes and chronic kidney disease are at high risk for kidney failure, cardiovascular events, and death. Whether treatment with semaglutide would mitigate these risks is unknown.
Methods: We randomly assigned patients with type 2 diabetes and chronic kidney disease (defined by an estimated glomerular filtration rate [eGFR] of 50 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio [with albumin measured in milligrams and creatinine measured in grams] of >300 and <5000 or an eGFR of 25 to <50 ml per minute per 1.73 m2 and a urinary albumin-to-creatinine ratio of >100 and <5000) to receive subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo. The primary outcome was major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes. Prespecified confirmatory secondary outcomes were tested hierarchically.
Results: Among the 3533 participants who underwent randomization (1767 in the semaglutide group and 1766 in the placebo group), median follow-up was 3.4 years, after early trial cessation was recommended at a prespecified interim analysis. The risk of a primary-outcome event was 24% lower in the semaglutide group than in the placebo group (331 vs. 410 first events; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.88; P = 0.0003). Results were similar for a composite of the kidney-specific components of the primary outcome (hazard ratio, 0.79; 95% CI, 0.66 to 0.94) and for death from cardiovascular causes (hazard ratio, 0.71; 95% CI, 0.56 to 0.89). The results for all confirmatory secondary outcomes favored semaglutide: the mean annual eGFR slope was less steep (indicating a slower decrease) by 1.16 ml per minute per 1.73 m2 in the semaglutide group (P<0.001), the risk of major cardiovascular events 18% lower (hazard ratio, 0.82; 95% CI, 0.68 to 0.98; P = 0.029), and the risk of death from any cause 20% lower (hazard ratio, 0.80; 95% CI, 0.67 to 0.95, P = 0.01). Serious adverse events were reported in a lower percentage of participants in the semaglutide group than in the placebo group (49.6% vs. 53.8%).
Conclusions: Semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes in patients with type 2 diabetes and chronic kidney disease.
FLOW Trial Committees and Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024 Jul 11;391(2):109-121.

7. Semaglutide & MASH (Metabolic dysfunction–associated steatohepatitis (MASH).

Background: Semaglutide, a glucagon-like peptide-1 receptor agonist, is a candidate for the treatment of metabolic dysfunction-associated steatohepatitis (MASH).
Methods: In this ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial, we assigned 1197 patients with biopsy-defined MASH and fibrosis stage 2 or 3 in a 2:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo for 240 weeks. The results of a planned interim analysis conducted at week 72 involving the first 800 patients are reported here (part 1). The primary end points for part 1 were the resolution of steatohepatitis without worsening of liver fibrosis and reduction in liver fibrosis without worsening of steatohepatitis.
Results: Resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of the 534 patients in the semaglutide group and in 34.3% of the 266 patients in the placebo group (estimated difference, 28.7 percentage points; 95% confidence interval [CI], 21.1 to 36.2; P<0.001). A reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of the patients in the semaglutide group and in 22.4% of those in the placebo group (estimated difference, 14.4 percentage points; 95% CI, 7.5 to 21.3; P<0.001). Results for the three secondary outcomes that were included in the plan to adjust for multiple testing were as follows: combined resolution of steatohepatitis and reduction in liver fibrosis was reported in 32.7% of the patients in the semaglutide group and in 16.1% of those in the placebo group (estimated difference, 16.5 percentage points; 95% CI, 10.2 to 22.8; P<0.001). The mean change in body weight was -10.5% with semaglutide and -2.0% with placebo (estimated difference, -8.5 percentage points; 95% CI, -9.6 to -7.4; P<0.001). Mean changes in bodily pain scores did not differ significantly between the two groups. Gastrointestinal adverse events were more common in the semaglutide group.
Conclusions: In patients with MASH and moderate or advanced liver fibrosis, once-weekly semaglutide at a dose of 2.4 mg improved liver histologic results.
ESSENCE Study Group. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. N Engl J Med. 2025 Jun 5;392(21):2089-2099.

8. Semaglutide & osteoarthritis

Background: Weight reduction has been shown to alleviate symptoms of osteoarthritis of the knee, including pain. The effect of glucagon-like peptide-1 receptor agonists on outcomes in knee osteoarthritis among persons with obesity has not been well studied.
Methods: We conducted a 68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. Participants with obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counseling on physical activity and a reduced-calorie diet. The primary end points were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores reflecting worse outcomes) from baseline to week

68. A key confirmatory secondary end point was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2 (on a scale of 0 to 100, with higher scores indicating greater well-being).
Results: A total of 407 participants were enrolled. The mean age was 56 years, the mean BMI 40.3, and the mean WOMAC pain score 70.9. A total of 81.6% of the participants were women. The mean change in body weight from baseline to week 68 was -13.7% with semaglutide and -3.2% with placebo (P<0.001). The mean change in the WOMAC pain score at week 68 was -41.7 points with semaglutide and -27.5 points with placebo (P<0.001). Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points vs. 6.5 points; P<0.001). The incidence of serious adverse events was similar in the two groups. Adverse events that led to permanent discontinuation of the trial regimen occurred in 6.7% of the participants in the semaglutide group and in 3.0% in the placebo group, with gastrointestinal disorders being the most common reason for discontinuation.
Conclusions: Among participants with obesity and knee osteoarthritis with moderate-to-severe pain, treatment with once-weekly injectable semaglutide resulted in significantly greater reductions in body weight and pain related to knee osteoarthritis than placebo.
Glucagon-like peptide-1 receptor agonists and osteoarthritis. N Engl J Med. 2024;391(17):1643–1644

9. Tirzepatide & Obstructive Sleep Apnea

Background: Obstructive sleep apnea is characterized by disordered breathing during sleep and is associated with major cardiovascular complications; excess adiposity is an etiologic risk factor. Tirzepatide may be a potential treatment.
Methods: We conducted two phase 3, double-blind, randomized, controlled trials involving adults with moderate-to-severe obstructive sleep apnea and obesity. Participants who were not receiving treatment with positive airway pressure (PAP) at baseline were enrolled in trial 1, and those who were receiving PAP therapy at baseline were enrolled in trial 2. The participants were assigned in a 1:1 ratio to receive either the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo for 52 weeks. The primary end point was the change in the apnea-hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) from baseline. Key multiplicity-controlled secondary end points included the percent change in AHI and body weight and changes in hypoxic burden, patient-reported sleep impairment and disturbance, high-sensitivity C-reactive protein (hsCRP) concentration, and systolic blood pressure.
Results: At baseline, the mean AHI was 51.5 events per hour in trial 1 and 49.5 events per hour in trial 2, and the mean body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) was 39.1 and 38.7, respectively. In trial 1, the mean change in AHI at week 52 was -25.3 events per hour (95% confidence interval [CI], -29.3 to -21.2) with tirzepatide and -5.3 events per hour (95% CI, -9.4 to -1.1) with placebo, for an estimated treatment difference of -20.0 events per hour (95% CI, -25.8 to -14.2) (P<0.001). In trial 2, the mean change in AHI at week 52 was -29.3 events per hour (95% CI, -33.2 to -25.4) with tirzepatide and -5.5 events per hour (95% CI, -9.9 to -1.2) with placebo, for an estimated treatment difference of -23.8 events per hour (95% CI, -29.6 to -17.9) (P<0.001). Significant improvements in the measurements for all prespecified key secondary end points were observed with tirzepatide as compared with placebo. The most frequently reported adverse events with tirzepatide were gastrointestinal in nature and mostly mild to moderate in severity.
Conclusions: Among persons with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes.
SURMOUNT-OSA Investigators. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med. 2024;391(25):1193–1205

10. Semaglutide & ASCVD (no T2D)

Background: Semaglutide, a glucagon-like peptide-1 receptor agonist, has been shown to reduce the risk of adverse cardiovascular events in patients with diabetes. Whether semaglutide can reduce cardiovascular risk associated with overweight and obesity in the absence of diabetes is unknown.
Methods: In a multicenter, double-blind, randomized, placebo-controlled, event-driven superiority trial, we enrolled patients 45 years of age or older who had preexisting cardiovascular disease and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 27 or greater but no history of diabetes. Patients were randomly assigned in a 1:1 ratio to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis. Safety was also assessed.
Results: A total of 17,604 patients were enrolled; 8803 were assigned to receive semaglutide and 8801 to receive placebo. The mean (±SD) duration of exposure to semaglutide or placebo was 34.2±13.7 months, and the mean duration of follow-up was 39.8±9.4 months. A primary cardiovascular end-point event occurred in 569 of the 8803 patients (6.5%) in the semaglutide group and in 701 of the 8801 patients (8.0%) in the placebo group (hazard ratio, 0.80; 95% confidence interval, 0.72 to 0.90; P<0.001). Adverse events leading to permanent discontinuation of the trial product occurred in 1461 patients (16.6%) in the semaglutide group and 718 patients (8.2%) in the placebo group (P<0.001).
Conclusions: In patients with preexisting cardiovascular disease and overweight or obesity but without diabetes, weekly subcutaneous semaglutide at a dose of 2.4 mg was superior to placebo in reducing the incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke at a mean follow-up of 39.8 months.
SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. NEJM 2023;389(22):2221–2232.

SGLT2 Inhibitors

11. SGLT2i & MACES

SGLT2i & MACES | Individual Trials							
Drug Yr	**T2D**	**Duration (yrs)**	**% Δ MACE**	**% Δ CHF endpoints**	**% Δ Mortality**	**% Δ Hypoglycemia**	**% Δ A1c**
Empagliflozin (NEJM 2015)	100%	3.1	1.6	1.4	2.6	0.1	0.24%
Canagliflozin (NEJM 2017)	100%	3.6	4.6	3.2	NS	3.6	0.58%
Dapagliflozin (NEJM 2019)	100%	4.2	NS	0.9	NS	0.3	0.42%
Dapagliflozin | HFrEF (NEJM 2019)	42%	1.5	1.9%	4.9	2.3		0.24%
Empagliflozin | HFrEF (NEJM 2020)	50%	1.3	NS	5.1	NS	0.1	0.16%
Dapagliflozin | CKD (NEJM 2020)	67%	2.4	1.8	1.8	2.1	0.6	-
Empagliflozin | HFpEF (NEJM 2021)	49%	2.2	0.9	3.2	NS	0.2	0.19%

12. SCLT2 inhibitors and renal outcomes

SGLT2i & Renal Outcomes						
Drug Yr	**T2D**	**RAS Inhibitor**	**Duration**	**Δ GFR endpoints (HR)**	**Δ Mortality**	**Baseline eGFR**
Empagliflozin | T2D + CKD (NEJM 2016)	100%	80%	3.1	0.61		48 - 83
Canagliflozin | T2D (NEJM 2017)	100%	80%	3.6	0.6	2.2%	76
Dapagliflozin | T2D (NEJM 2019)	100%	81%	4.2	0.76	0.4%	85
Canagliflozin | T2D + CKD (NEJM 2019)	100%	80%	2.6	0.68	1.5%	56 X
Empagliflozin | HFrEF (NEJM 2020)	49%	80%	1.3	0.50	0.8%	61 X
Dapagliflozin | CKD (NEJM 2020)	67%	98%	2.4	0.61	2.1%	43 X (13% eGFR 20-29)
Empagliflozin | CKD (NEJM 2023)	46%	85%	2.0	0.71	0.6%	37 (30% eGFR 20-29)

The evolution of recent ADA guidance on pharmacotherapy

2025 ADA guidelines for T2D pharmacologic treatment

For the past 4 years the ADA has *removed metformin as a 1st line therapy for patients with T2D*.

An evolution of this change is apparent in a review of the treatment annual algorithm published by the ADA: 1) 2021 "First-line therapy is metformin…" 2) 2022 First-line therapy "…generally includes metformin…" 3) 2023-2024 there is no mention of metformin as 1st line therapy
Additionally, the title of the algorithm has changed from 2022: "Pharmacologic Treatment of Hyperglycemia in Adults with Type 2 Diabetes"; to 2024 "Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes" (note they removed the word "hyperglycemia" from the title, emphasizing that the choice of *which medications to use* is now the focus of the algorithm.
As noted, this has occurred as a result of dozens of RCTs over the past 8+ years assessing clinical outcomes of SGLT2 inhibitors (primarily heart failure and renal) and GLP1 agonists (primarily ASCVD) | As noted above

ADA Snippets – 2025 (my take on useful but maybe under the radar guidance)

In people with heart failure, chronic kidney disease, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 receptor agonist or a SGLT-2 inhibitor with proven benefits should be made irrespective of background use of metformin or A1C.

Agents with proven benefits

	CV Effects		Kidney Effects	MASH Effects
	MACE	**HF**	**Progression of CKD**	
SGLT2 inhibitors	canagliflozin empagliflozin	canagliflozin empagliflozin dapagliflozin ertugliflozin	canagliflozin empagliflozin dapagliflozin	Unknown
GLP-1 RAs	Dulaglutide liraglutide semaglutide	Neutral	Albuminuria Dulaglutide liraglutide semaglutide	Potential benefit
			CKD progression semaglutide	
Dual GIP & GLP-1 RA	Under investigation	Under investigation	Under investigation	Potential benefit

Canagliflozin (Invokana ®) | Empagliflozin (Jardiance ®) | Dapagliflozin (Farxiga ®)
Ertugliflozin (Steglatro ®) | Dulaglutide (Trulicity®) | Liraglutide (Victoza®) semaglutide (Ozempic® – SC; Rybelsus® - oral)

Modified from:Table 9.2 2025 Standards of Care

Aside from weight loss there are slight but nuances differences in disease oriented outcomes between GLP-1 RA and SGLT2 inhibitors

	GLP-1 RA	SGLT2i
MACE	X	X
CV Death	X	X
All-cause mortality	X	X
MI	X	X
Kidney endpoints	X	X
CVA	X	
Heart failure hospitalizations		X

American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2025. ***Diabetes Care*. 2025;48(Suppl 1):S181–S206**.

Combined Therapy Option:

- Consider combining a GLP-1 RA + SGLT2 inhibitor (both with demonstrated CV benefit) in patients with:
- Established ASCVD or
- Multiple ASCVD risk factors
- → For additive reduction in CV and kidney events

Bottom-Line

- GLP-1 agonists (& SGLT2 inhibitors) have taken over center stage in the ADA standards of care (for good reason) but the landscape on these classes of medications is changing rapidly

Supplemental Content

More snippets from the 2025 ADA Recommendations – Glycemic Management in T2D

- **Initial Therapy**
  - **Start with combination therapy** at diagnosis when appropriate to reach individualized A1C goals faster.

- **Cardiovascular Disease (ASCVD)**
  - **In established or high-risk ASCVD:**
    - Use a **GLP-1 RA and/or SGLT2 inhibitor** with proven CV benefit.
    - Therapy should be considered **regardless of A1C** to reduce CV events.

- **Heart Failure (HF)**
  - **In HFrEF or HFpEF:**
    - Use an **SGLT2 inhibitor** to lower glucose and reduce HF hospitalizations, regardless of A1C.
  - **In HFpEF with obesity:**
    - Use a **GLP-1 RA** with demonstrated symptom improvement and weight benefit, regardless of A1C.

- **Chronic Kidney Disease (CKD)**
  - **In CKD (eGFR 20–60 or albuminuria):**
    - Use an **SGLT2 inhibitor or GLP-1 RA** with renal and CV benefit.
    - Note: **SGLT2 inhibitors are less effective for glucose lowering at eGFR <45**.
  - **In advanced CKD (eGFR <30):**
    - Prefer a **GLP-1 RA** for glycemic control and lower hypoglycemia risk.

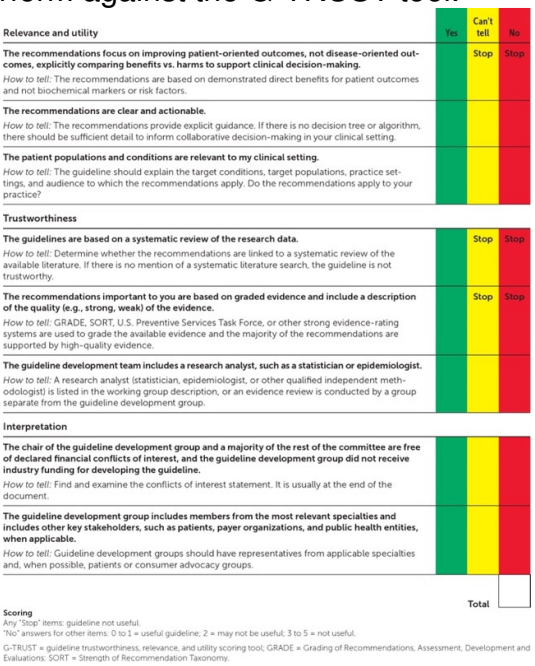
- **MASLD / MASH (Metabolic Liver Disease)**
  - **In MASLD with overweight/obesity:**
    - Consider a **GLP-1 RA or dual GIP/GLP-1 RA** to improve glycemia and support weight loss.
  - **In biopsy-proven MASH or high fibrosis risk:**
    - Prefer **pioglitazone, a GLP-1 RA, or dual GIP/GLP-1 RA** for glycemic management and liver benefit.

- **Medication Combinations and Insulin Use**
  - **Avoid DPP-4 inhibitors with GLP-1 RA or dual GIP/GLP-1 RA** due to lack of added benefit.
  - **If no insulin deficiency:**
    - Prefer **GLP-1 RA or dual GIP/GLP-1 RA** over insulin.
  - **If insulin is used:**
    - Combine with a **GLP-1 RA or dual GIP/GLP-1 RA** to improve glycemia, reduce hypoglycemia risk, and support weight loss.
    - **Reassess insulin dosing** when adding or adjusting GLP-1 RA therapy.

Objectives: At the end of this session, the participant will be able to:

- Discuss what makes a "guideline we can trust"
- Discuss why guidelines might be discordant
- Summarize several recent practice guidelines as examples

In July 2018, the National Guideline Clearinghouse (NGC) was shut down because the contract that supported it expired. It has since been replaced by the Emergency Care Research Institute (ECRI) Guidelines Trust (https://guidelines.ecri.org/). Its website has undergone many changes and additional changes are ongoing, including its Guideline Summaries which provide a snapshot of guidelines and how well they perform against the G-TRUST tool.



Relevance and utility	Yes	Can't tell	No
The recommendations focus on improving patient-oriented outcomes, not disease-oriented outcomes, explicitly comparing benefits vs. harms to support clinical decision-making. *How to tell:* The recommendations are based on demonstrated direct benefits for patient outcomes and not biochemical markers or risk factors.		Stop	Stop
The recommendations are clear and actionable. *How to tell:* The recommendations provide explicit guidance. If there is no decision tree or algorithm, there should be sufficient detail to inform collaborative decision-making in your clinical setting.			
The patient populations and conditions are relevant to my clinical setting. *How to tell:* The guideline should explain the target conditions, target populations, practice settings, and audience to which the recommendations apply. Do the recommendations apply to your practice?			
Trustworthiness			
The guidelines are based on a systematic review of the research data. *How to tell:* Determine whether the recommendations are linked to a systematic review of the available literature. If there is no mention of a systematic literature search, the guideline is not trustworthy.		Stop	Stop
The recommendations important to you are based on graded evidence and include a description of the quality (e.g., strong, weak) of the evidence. *How to tell:* GRADE, SORT, U.S. Preventive Services Task Force, or other strong evidence-rating systems are used to grade the available evidence and the majority of the recommendations are supported by high-quality evidence.		Stop	Stop
The guideline development team includes a research analyst, such as a statistician or epidemiologist. *How to tell:* A research analyst (statistician, epidemiologist, or other qualified independent methodologist) is listed in the working group description, or an evidence review is conducted by a group separate from the guideline development group.			
Interpretation			
The chair of the guideline development group and a majority of the rest of the committee are free of declared financial conflicts of interest, and the guideline development group did not receive industry funding for developing the guideline. *How to tell:* Find and examine the conflicts of interest statement. It is usually at the end of the document.			
The guideline development group includes members from the most relevant specialties and includes other key stakeholders, such as patients, payer organizations, and public health entities, when applicable. *How to tell:* Guideline development groups should have representatives from applicable specialties and, when possible, patients or consumer advocacy groups.			
			Total

Scoring
Any "Stop" items: guideline not useful.
"No" answers for other items: 0 to 1 = useful guideline; 2 = may not be useful; 3 to 5 = not useful.

G-TRUST = guideline trustworthiness, relevance, and utility scoring tool; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; SORT = Strength of Recommendation Taxonomy.

Uncensored Guidelines

The current administration has shut down or censored many sources of recommendations upon which clinicians have depended; especially those dealing with reporoductive rights and the care of LGBTQ+ persons. Fortunately, the American Academy of Family Physicians has a well-maintained web site that includes guidelines and resources for caring for ***all*** our patients: https://www.aafp.org/family-physician/patient-care/clinical-recommendations.html.

Discordant guidelines

Most clinicians have encountered conflicting guideline recommendations. Barry and colleagues proposed the following as the most likely causes of discordant guidelines:

- **Interpretation**: The developers of the guidelines value some outcomes more than others.
- **Speculation**: When evidence is lacking, experts provide their best guess.
- **Extrapolation**: Recommendations extrapolate beyond the research, whether to specific interventions (e.g., blood pressure targets) or the study populations.
- **Representation**: The panel of developers lacks relevant stakeholders (e.g., patients, primary care clinicians).
- **Oversimplification**: Guidelines apply a one-size-fits-all approach that ignores nuances about disease severity, patient comorbidity, age, and other contextual factors.
- **Overcomplication**: Guidelines address too many specific questions.

- **Application**: Guidelines do not consistently address feasibility and lack clarity on whether they apply to individuals or systems.
- **Money**: Developers have conflicts of interest, or they do not address the costs of guideline implementation.

Barry HC, Cosgrove L, Slawson DC. Where Clinical Practice Guidelines Go Wrong. Am Fam Physician. Apr 1 2022;105(4):350-352.

What should clinicians do?

- Be skeptical.
- Find a source of guidelines that follow good practices such as AAFP, ACP, NICE, or ECRI
- Apply the most conservative, least interventional, guidelines first
- You probably are stuck knowing the guidelines that “everybody is talking about”
- Be a leader – work with your practice group, institution to use the G-TRUST tool and then refine guidelines for local use

1. Calcium score: what do the most reliable guidelines recommend? An analysis using the G-TRUST tool

INTRODUCTION: In 2023, cardiovascular disease was the leading cause of death worldwide. Various risk calculation tools based on risk factors can be used to estimate this risk. Calculating the coronary calcium score should allow us to assess this risk at an individual level. There is no consensus in the various good clinical practice guidelines (CPG) on the use of this score. The aim of this study was to assess the reliability of the various CPGs for the use of the calcium score in primary prevention. **METHODS:** CPGs published between 2018 and 2023 whose recommendations included advice on the use of CSC in primary prevention cardiovascular risk assessment for the general population was searched via Pubmed. The G-TRUST evaluation grid was then applied to the CPGs to determine which fell into the "reliable and relevant" category. **RESULTS:** 467 publications were identified via Pubmed. Only seven met the inclusion criteria. Of these seven CPGs, only two obtained an overall score of "reliable and relevant." The other five were assessed as "not usable" because of the risk of conflicts of interest, the absence of a systematic review, or the absence of patients' opinions and wishes. **DISCUSSION:** The two CPGs selected as reliable and relevant recommended that the CSC should not be used to assess cardiovascular risk, while the five classified as "not usable" recommended its use. G-TRUST is a tool which assesses the quality of the design of a recommendation and not the quality of the guidelines they propose.
Vincent YM, Gocko X, Francois C, Supper I, Cauchon M, Boussageon R. Calcium score: what do the most reliable guidelines recommend? An analysis using the G-TRUST tool. Fam Pract. Oct 21 2025;42(6)doi:10.1093/fampra/cmaf079

The overall quality of guidelines and guideline development processes have generally improved and we see fewer guidelines that are driven purely by expert opinion. These expert guidelines probably play a role when research is lacking, such as this guideline on managing patients with cancer pain and concommittant substance abuse.

2. Expert panels: Continue opioids but increase monitoring for patients with cancer-related pain who also use nonmedical stimulants

Clinical question: How should clinicians manage pain in patients with cancer-related pain who also use nonmedical stimulants (eg, cocaine or methamphetamine)?
Study design: Practice guideline
Funding source: Foundation
Setting: Outpatient (any)
Synopsis: This is a classic example of a BOGSAT.* The authors convened groups of palliative care and addiction experts (62% were women, 78% were white, and 96% were physicians) and conducted 2 modified Delphi panels to figure out what to do with patients with cancer pain who also take nonmedical stimulants. Both panels addressed patients with advanced cancer (metastatic/noncurable/noncontrolled by treatment), but one panel addressed patients with a mortality prognosis of weeks to months and the other addressed patients with more favorable prognoses (months to years). They used 3 rounds of fairly standard Delphi methods, but they do not describe adhering to the guideline development processes espoused by the National Academy of Medicine (formerly the Institute of Medicine) and other groups (such as looking for actual studies to guide their recommendations, the inclusion of patients, and addressing conflicts of interest). Although it is likely that the evidence base is quite limited, the other guideline processes could have been incorporated.
Overall, the panels agreed that using opioids for pain control should continue regardless of prognosis in patients with advanced cancer, but for those with more favorable prognoses, the panel supports ongoing opioids “so long as stimulant use was not an ongoing issue.” So, monitoring the patients for ongoing stimulant use was another important component. Additionally, regardless of prognosis, the panels agreed that it was inappropriate to taper opioids, that doing so would be cruel or punitive. For patients with short prognoses, the panel recommended not changing to buprenorphine/naloxone, but they were uncertain about doing this for patients with longer prognoses. The panel also recommends counseling patients about the harms of stimulant use. Finally, the

panels recommend transitioning to buprenorphine for the management of pain in patients with persistent misuse — not as a treatment for addiction, but as a safer opioid for the management of pain.
*Bunch of Old Guys/Gals Sitting Around Talking
Bottom line: This consensus guideline suggests that when faced with a patient with advanced cancer and pain (regardless of prognosis) who also takes nonmedical stimulants, clinicians should continue opioids without tapering, increase monitoring, and not change to buprenorphine/naloxone. The panel recommends switching to buprenorphine for the management of pain in patients with persistent misuse, not as a treatment for addiction, but as a safer opioid for the management of pain. The panel displayed a refreshing focus on the comfort of these patients. (LOE = 5)
Jones KF, Khodyakov D, Han BH, et al. Expert consensus-based guidance on approaches to opioid management in individuals with advanced cancer-related pain and nonmedical stimulant use. Cancer 2023;129(24):3978-3986.

Recent Evidence-based Guidelines

3. Management of opioid use disorder

Background: In an evolving landscape of practices and policies, reviewing and incorporating the latest scientific evidence is necessary to ensure optimal clinical management for people with opioid use disorder. We provide a synopsis of the 2024 update of the 2018 National Guideline for the Clinical Management of Opioid Use Disorder, from the Canadian Research Initiative in Substance Matters.
Methods: For this update, we followed the United States Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines and used the Appraisal of Guidelines Research and Evaluation-Recommendation Excellence tool to ensure guideline quality. We carried out a comprehensive systematic literature review, capturing the relevant literature from Jan. 1, 2017, to Sept. 14, 2023. We drafted and graded recommendations according to the Grading of Recommendations, Assessments, Development and Evaluation approach. A multidisciplinary external national committee, which included people with living or lived experience of opioid use disorder, provided input that was incorporated into the guideline.
Recommendations: From the initial 11 recommendations in the 2018 guideline, 3 remained unchanged, and 8 were updated. Specifically, 4 recommendations were consolidated into a single revised recommendation; 1 recommendation was split into 2; another recommendation was moved to become a special consideration; and 2 recommendations were revised. Key changes have arisen from substantial evidence supporting that methadone and buprenorphine are similarly effective, particularly in reducing opioid use and adverse events, and both are now considered preferred first-line treatment options. Slow-release oral morphine is recommended as a second-line option. Psychosocial interventions can be offered as adjunctive treatment but should not be mandatory. The guideline reaffirms the importance of avoiding withdrawal management as a standalone intervention and of incorporating evidence-based harm reduction services along the continuum of care.
Interpretation: This guideline update presents new recommendations based on the latest literature for standardized management of opioid use disorder. The aim is to establish a robust foundation upon which provincial and territorial bodies can develop guidance for optimal care.
Yakovenko I, Mukaneza Y, Germe K, et al. Management of opioid use disorder: 2024 update to the national clinical practice guideline. CMAJ. Nov 11 2024;196(38):E1280-E1290. doi:10.1503/cmaj.241173

4. ASCO Guideline: Cannabis and Cannabinoids in Adults With Cancer

PURPOSE: To guide clinicians, adults with cancer, caregivers, researchers, and oncology institutions on the medical use of cannabis and cannabinoids, including synthetic cannabinoids and herbal cannabis derivatives; single, purified cannabinoids; combinations of cannabis ingredients; and full-spectrum cannabis. **METHODS:** A systematic literature review identified systematic reviews, randomized controlled trials (RCTs), and cohort studies on the efficacy and safety of cannabis and cannabinoids when used by adults with cancer. Outcomes of interest included antineoplastic effects, cancer treatment toxicity, symptoms, and quality of life. PubMed and the Cochrane Library were searched from database inception to January 27, 2023. ASCO convened an Expert Panel to review the evidence and formulate recommendations. **RESULTS:** The evidence base consisted of 13 systematic reviews and five additional primary studies (four RCTs and one cohort study). The certainty of evidence for most outcomes was low or very low. **RECOMMENDATIONS:** Cannabis and/or cannabinoid access and use by adults with cancer has outpaced the science supporting their clinical use. This guideline provides strategies for open, nonjudgmental communication between clinicians and adults with cancer about the use of cannabis and/or cannabinoids. Clinicians should recommend against using cannabis or cannabinoids as a cancer-directed treatment unless within the context of a clinical trial. Cannabis and/or cannabinoids may improve refractory, chemotherapy-induced nausea and vomiting when added to guideline-concordant antiemetic regimens. Whether cannabis and/or cannabinoids can improve other supportive care outcomes remains uncertain. This guideline also highlights the critical need for more cannabis and/or cannabinoid research. Additional information is available at www.asco.org/supportive-care-guidelines.
Braun IM, Bohlke K, Abrams DI, et al. Cannabis and Cannabinoids in Adults With Cancer: ASCO Guideline. J Clin Oncol. May 1 2024;42(13):1575-1593. doi:10.1200/JCO.23.02596

5. American College of Physicians urges caution when patients want to use cannabis/cannabinoids to treat chronic noncancer pain

Clinical question: What advice should be given to patients who are using, or wish to use, cannabis or cannabinoid-containing products to decrease chronic noncancer pain?
Study design: Practice guideline **Funding source:** Self-funded or unfunded
Synopsis: This “advice” differs from typical practice guidelines (which this group also produces) by using systematic reviews and practice guidelines developed by others and attempts to answer questions for which evidence is uncertain or emerging or practice does not follow the evidence. These statements, unlike many guidelines, also consider the relative value of one approach over another. This

advice attempts to provide bounded (by current evidence) expert advice, in this case, for cannabis or cannabinoid use among patients with chronic noncancer pain. The advice suggests warning the following patients that the risk of harm could outweigh benefit: those who are pregnant, breastfeeding, or trying to conceive; adolescents and young adults; people with current or past substance use disorder; patients with serious mental illness; and patients at risk for falling. For other patients who are not in these groups, the advice suggests discussing the currently known benefits and risks of cannabis or cannabinoids. Current evidence suggests a small benefit, and the long-term adverse effects of chronic use are not established. Encourage patients to try other approaches first.
Bottom line: The evidence is sparse regarding the use of cannabis or cannabinoids for chronic noncancer pain and this "advice" (which is different from a more rigid guideline) attempts, in a conservative way, to fill in the gaps. The authors suggest cautioning patients who are at risk of harm — young people, old people, pregnant people, and those with a current or past substance use disorder — to avoid these products. Let other patients know that the current evidence suggests only a small likelihood of benefit. (LOE = 5)
Kansagara D, Hill KP, Yost J, et al. Cannabis or cannabinoids for the management of chronic noncancer pain: Best practice advice from the American College of Physicians. Ann Intern Med 2025 May;178(5):714-724.

6. Misleading guideline from the American Academy of Neurology on using epidural steroid injections in adults

Clinical question: Are epidural steroid injections effective in alleviating pain in adults with radicular pain and spinal stenosis?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Foundation
Synopsis: The American Academy of Neurology (AAN) usually follows modern guideline development methods, but this guideline is a notable departure from that quality level. The AAN convened a panel to conduct a systematic review of randomized trials to drive the development of a guideline on using epidural steroid injections (ESIs) for treating adults with spinal stenosis and radiculopathies. The panel included methodologists and clinicians with expertise in pain management, anesthesiology, and back pain. They used an explicit process for addressing financial conflict of interest but are silent about intellectual conflict of interest. In the appendix, the clinicians on the panel are described as experts in ESI. The panel defined short-term (3 months or less) and long-term outcomes (6 months or longer). They recognized the paucity of data on longer-term outcomes. In addition to assessing the effect sizes for pain and for disability, the authors also defined "success rate differences" as the proportion having "more favorable outcomes." If, on average, a study reported that injections provided an improvement, but the effect size was miniscule, they would still count that as a success. I would have preferred that they limited their definition to include only moderate or large effect sizes as these are more likely to be clinically meaningful. Ultimately, the authors included 90 randomized trials with an unknown number of participants. They report assessing each study's risk of bias using the AAN's classification scheme rather than an externally validated tool such as the Cochrane Risk of Bias tool. Ultimately, the only data they report are numbers needed to treat, all of which were in single digits (which would be admirable if the data really meant something important). They claim that since adverse events were rare, they only reported them in narrative form and go on to state the rates of harms ranged from 2.4% to 16.8%. With 90 trials (and an unstated number of participants), it is possible that serious events were, in fact, rare, but it would have been nice to have the actual data. The selective reporting of harms along with their interpretation of benefit all can be explained by their intellectual conflicts of interest.
Bottom line: The data underlying this guideline are not to be believed. Implying a large benefit without addressing clinically important improvement is irresponsible and self-serving
Armon C, Narayanaswami P, Potrebic S, et al. Epidural steroids for cervical and lumbar radicular pain and spinal stenosis systematic review summary: Report of the AAN Guidelines Subcommittee. Neurology 2025;104(5):e213361.

7. Do not use injections or radiofrequency to treat chronic neck or low back pain

Clinical question: What interventions should not be used for patients with chronic neck or low back pain?
Study design: Practice guideline
Funding source: Foundation
Synopsis: These guidelines are based on a systematic review and network meta-analysis of randomized trials and a systematic review of observational studies of interventional procedures for axial and radicular, chronic, noncancer spine (cervical and lower back) pain. The development group included patients, clinicians, and methodologists. No members had financial conflicts of interest. For localized chronic low back or cervical pain, the group recommends against epidural or joint injection of a steroid, local anesthetic, or both; joint radiofrequency ablation; or intramuscular injection of a local anesthetic, with or without a steroid. For radicular cervical or low back pain, they recommend against using dorsal root ganglion radiofrequency or epidural injection of steroid, local anesthetic, or both. The group considered recommending treatments with moderate to high certainty evidence of harms or burden if there was moderate or high certainty evidence of important benefit. However, they were unable to find evidence of benefit as compared with placebo or sham procedures for any of the evaluated interventions, and their recommendations are considered strong (high confidence that the intervention will produce more harm than benefit). I am a little concerned because "did not work better than placebo" is not the same as "did not work," since there frequently is a profound response to placebo treatments of pain — and, whether placebo or real treatment is the cause, better is better. The meta-analysis did not report on response rates in the comparator groups so it's difficult to know.
Bottom line: These guidelines strongly recommend against the use of corticosteroid and/or local anesthetic injection or radiofrequency ablation to treat chronic low back or cervical spine pain not due to cancer.
Busse JW, Genevay S, Agarwal A, et al. Commonly used interventional procedures for non-cancer chronic spine pain: A clinical practice guideline. BMJ 2025;388:e079970.

8. Imaging guidelines for children with mild traumatic brain injury (concussion)

Clinical question: What are current clinical practice guidelines for imaging children with acute mild traumatic brain injury (concussion)?
Study design: Systematic review **Setting:** Various (meta-analysis)
Synopsis: These investigators searched 4 databases, including Cochrane Central, and identified 11 clinical practice guidelines that

provide guidance for the management of children with acute mild traumatic brain injury (mTBI). Pairs of reviewers selected guidelines for inclusion and extracted their recommendation. They determined the quality of evidence supporting each of the guidelines and evaluated the applicability of the guidelines to emergency management. Six of the guidelines were rated as high quality.
The investigators identified 34 recommendations based on moderate- to high-quality evidence. Routine imaging is not recommended. Consider computed tomography (CT) of the head or neck for children in whom injury is suspected. Consider head CT for children with severe headache, following clinical decision-making rules. Children with acutely worsening symptoms should have immediate imaging. Don't use skull radiographs for screening or to diagnose mTBI in children.
Bottom line: In children with acute mTBI, commonly called concussion, the best evidence suggests considering head CT only for children with severe headache, worsening symptoms, or in whom a head or neck injury is also suspected. Skull x-rays do not have a role in mTBI management, and routine imaging is also not supported by high-quality evidence.
Moore L, Ben Abdeljelil A, Tardif PA, et al. Clinical practice guideline recommendations in pediatric mild traumatic brain injury: a systematic review. Ann Emerg Med 2024;83(4):327-339.

9. Contact children of abused children should be formally evaluated

Clinical question: What evaluations should contact children of abused children undergo?
Study design: Practice guideline
Funding source: Unknown/not stated
Setting: Various (guideline)
Synopsis: Members of the International Consensus Group on Contact Screening in Suspected Child Physical Abuse used systematic reviews to guide the development of consensus guidelines on managing contact children when another child is suspected of having been physically abused. The guideline applies to contact children younger than 5 years. A contact child is defined as asymptomatic and either a sibling, household member, or in the same care setting as the abused child. The panel recommends a formal history and physical examination of all contact children. If any positive findings are elicited (or in any subsequent assessments), then a formal report and investigation is needed. If nothing indicating abuse is found *and* the child is older 2 years, the panel recommends no further assessment. If the child is younger than 1 year, the panel recommends magnetic resonance imaging (MRI) of the brain (followed by a spine MRI if the brain MRI result is abnormal), plus a full skeletal survey. For this age group, the panel also recommends limited-view skeletal surveys at 11 to 14 days if the initial survey identifies equivocal or abnormal findings and a follow-up MRI if the initial one is abnormal. For children 1 to 2 years of age, the panel recommends a full skeletal survey with limited-view skeletal surveys at 11 to 14 days if the initial survey identifies equivocal or abnormal findings.
Bottom line: Contact children under 5 years should undergo a history and physical examination. Children younger than 12 months should have an MRI and skeletal survey. Children 12 months to 24 months of age should have a skeletal survey. No routine imaging is indicated in asymptomatic children older than 24 months. Children with positive findings should be investigated as an abused child.
Mankad K, Sidpra J, Mirsky DM, et al. International consensus statement on the radiological screening of contact children in the context of suspected child physical abuse. JAMA Pediatr 2023;177(5):526-533.

10. AAP Practice guideline on children with obesity

Clinical question: How should we manage excess weight in children?
Study design: Practice guideline
Setting: Various (guideline)
Synopsis: These guidelines were based on 2 systematic reviews of the literature of the effect of weight on the morbidity of children and the effectiveness of treatment. The guidelines represent policy statements, as much as specific recommendations; emphasize the societal, community, family, and individual contributions that promote unhealthy weight in children; and suggest addressing those contributions when possible. Here is a brief overview of their consensus recommendations.

- Use body mass index to annually track the weight of children two years or older and to identify and monitor children who are overweight or obese.
- Try to avoid stigmatizing children by using careful language: ask if you can discuss weight; avoid the use of "obese child," instead say "the child with obesity"; and avoid words known to be offensive, such as obese, morbidly obese, large, fat, overweight, and chubby. Instead, focus on the effects of weight on health by saying "unhealthy weight" or "gaining too much weight for their age, height, or health."
- Consider lipid testing in children younger than 10 years with obesity.
- Check blood pressure at every visit in children with unhealthy weight.
- Check fasting lipids, hemoglobin A1c for diabetes or prediabetes, and alanine transaminase for nonalcoholic fatty liver in children 10 years or older with obesity.

Their treatment recommendations are less prescriptive and emphasize a comprehensive approach that includes nonstigmatizing activities, including motivational interviews and the offer of intensive (at least 26 hours) health behavior and lifestyle treatment, which is a formal, longitudinal, multimodal approach to promote healthy behaviors. The authors suggest, for children at least 12 years of age, the consideration of pharmacologic therapy with or without the intensive health behavior and lifestyle treatment. They also suggest bariatric surgery for adolescents 13 years or older.
Bottom line: Following the lead of other organizations, the American Academy of Pediatrics has issued guidelines for treating excessive body weight in children and adolescents using a chronic disease model. They stress the need for early identification of comorbidities and interventions aimed at changing eating and activity habits through intensive behavior and lifestyle modification. They suggest considering medication or bariatric surgery in adolescents. They offer ways of talking about weight that will not stigmatize the children, though I'm skeptical that the focus on weight instead of health will prevent shaming. The focus on individual behavior instead of structural solutions may set up patients, parents, and clinicians for failure.
Hampl SE, Hassink SG, Skinner AC, et al. Clinical practice guideline for the evaluation and treatment of children and adolescents with obesity. Pediatrics 2023;151(2):e2022060640.

11. Canadian national guideline on pharmacotherapy to treat obesity

Clinical question: How can pharmacotherapy best be used to assist patients in treating obesity?
Study design: Practice guideline **Funding source:** Foundation
Synopsis: This guideline was created by primary care physicians, obesity specialists, and patients based on a systematic review of relevant literature. It is an update to a similar 2020 guideline, but much has happened since then in the world of -tides and -flozins. The primary sponsor of this guideline creation was Obesity Canada, a patient-advocacy group, which may create some degree of intellectual bias and conflict of interest. Overall, however, the methodology was strong, with evidence-based recommendations that were peer reviewed. The guidelines recommend that any pharmacotherapy be implemented in conjunction with behavioral measures and lifestyle changes. Patients with a body mass index (BMI) of at least 30 (or at least 27 with obesity-related complications, such as diabetes, sleep apnea, hypertension) should consider one of the following medications: semaglutide, tirzepatide, liraglutide, naltrexone/bupropion, or orlistat. The same is true for those with type 2 diabetes mellitus. Evidence is strongest for semaglutide and tirzepatide. Long-term use of semaglutide, tirzepatide, liraglutide, or orlistat is endorsed if necessary to maintain weight loss. There are specific recommendations for patients with important comorbidities. Semaglutide is recommended for persons with atherosclerotic cardiovascular disease; tirzepatide (preferred) or semaglutide are recommended for those with heart failure; and liraglutide, orlistat, or tirzepatide are recommended for patients with prediabetes. Tirzepatide or liraglutide are recommended for patients with sleep apnea, while semaglutide is recommended preferentially for patients with osteoarthritis.
Bottom line: Pharmacotherapy with semaglutide, tirzepatide, liraglutide, naltrexone/bupropion, or orlistat is recommended for patients with a BMI of at least 30 (or at least 27 with obesity-related complications). Specific drugs are recommended for patients with comorbidities such as heart disease, heart failure, and sleep apnea.
Pedersen SD, Manjoo P, Dash S, Jain A, Pearce N, Poddar M. Pharmacotherapy for obesity management in adults: 2025 clinical practice guideline update. CMAJ 2025;197:E797-E809.

12. New US guidelines suggest risk-based approach to stage 1 hypertension

Clinical question: What does a coalition of medical societies recommend regarding the treatment of hypertension in adults?
Study design: Practice guideline
Funding source: Unknown/not stated
Setting: Various (guideline)
Synopsis: These guidelines are from the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines (Joint Committee), and a number of other professional associations, and they update the 2017 guidelines. These guidelines refer to blood pressure obtained by cuff only (oscillometric machines), which they recommend, rather than on auscultatory determination (so long, Korotkoff sounds), which results in higher readings. For patients who have been given a new diagnosis of hypertension (2 readings at separate occasions), they Joint Committee suggests obtaining, in addition to the usual labs, urine albumin (or protein)-to-creatinine ratio and a baseline electrocardiogram. The guidelines continue to recommend weight loss, a Dietary Approaches to Stop Hypertension (DASH) diet, alcohol abstinence, and sodium restriction, with consideration of potassium salt substitutes, which are associated with lower pressures. For stage 1 hypertension, they recommend drug treatment with the usual initial choices only for patients with a PREVENT-CVD score of at least 7.5% (get calculator at https://professional.heart.org/en/guidelines-and-statements/prevent-calculator). If the score is less than 7.5%, reassess blood pressure in 3 months to 6 months. If blood pressure is still elevated, start treatment. For secondary hypertension, start 2 drugs at the same time in a single-pill combination, such as an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker (ARB) combined with a thiazide or calcium channel blocker (CCB) to minimize side effects and improve adherence. The guidelines suggest more aggressive treatment of patients with diabetes or kidney disease; that is, immediately starting drug therapy for stage 1. The guidelines contain additional recommendations for specific patient populations.
Bottom line: These new guidelines offer a few tweaks to our approach: Use a machine, if you aren't already, to check blood pressures; use a new calculator (https://professional.heart.org/en/guidelines-and-statements/prevent-calculator) to decide whether to start drug treatment or a trial of lifestyle modification for stage 1 hypertension; consider adding dietary potassium; and start treating stage 2 with a low-dose combination of 2 drugs (ACE inhibitor or ARB plus a thiazide or CCB).
Writing Committee Members, Jones DW, Ferdinand KC, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension 2025;82(10):e212-e316.

Guideline implementation

Guideline implementation is typically absent from recommendations and, quite frankly, can feel unrealistic and onerous. It is unclear why this next guideline was published – it will require 3 or 4 additional office visits for each patient who screens positive, and for a condition with no really effective therapy.

13. Unrealistic recommendations on detecting cognitive impairment

Clinical question: Can a novel workflow facilitate detecting adults with cognitive impairment among older adults in primary care settings?
Study design: Practice guideline
Funding source: Foundation

Setting: Outpatient (primary care)
Synopsis: The National Academy of Neuropsychology hosted an interdisciplinary summit with multiple speakers and attended by representatives from national organizations. Several of the key recommendations from that summit address research priorities (and actually created a research network) and policy matters (eg, payment models). These authors present a novel workflow to improve detecting cognitive impairment in older adults seeking care in primary care settings. Although several of their recommendations make sense, ***be clear that most have actually not been tested in primary care.*** For example, their recommendations on criteria for the ideal screening tool make good sense: fast, easy to administer by untrained staff, high sensitivity (especially for detecting mild cognitive impairment) and assess the domains affected in the most common causes of dementia (i.e., memory and executive function). The first part of their novel approach includes applying electronic health record data to tools that risk-stratify patients: the Brief Dementia Screening Indicator or the Rapid Assessment of Dementia Risk. Each has been tested in community settings but have not been evaluated in primary care settings. They then recommend short cognitive screening testing in persons identified as high risk for dementia and those who have memory concerns independent of their risk stratification. For those who test positive, they then recommend 3 or 4 additional visits to complete the assessment. The first visit would use a longer cognitive assessment (eg, the Montreal Cognitive Assessment) and assess for conditions (eg, sleep disorders, depression, etc.) that affect cognition. The second visit is used to assess interval changes and to provide time to make referrals for additional testing (eg, sleep studies, imaging). The last visits would be used to review test results and arrange for additional consultations, if needed. While some of the processes make sense, the implementation seems cumbersome and expensive. Finally, these recommendations need formal assessment in the real world of clinical practice.
Bottom line: This panel from the National Academy of Neuropsychology recommends, to improve detecting older adults with cognitive impairment, using electronic health record data to "prescreen" adults at risk for dementia followed by using a formal screening test of cognition. For those with abnormal screening tests, the panel recommends an additional 3 to 4 primary visits for further assessment and coordination of care. Many of these recommendations have not been vetted in primary care settings and addresses a condition for which there is no effective treatment.
Hilsabeck RC, Perry W, Lacritz L, et al. Improving early detection of cognitive impairment in older adults in primary care clinics: Recommendations from an interdisciplinary geriatrics summit. Ann Fam Med 2024;22(6):543-549.

Finally, older studies have reinforced the lack of adequate time to deliver guideline-directed care. The following recent study revisited this issue. I'm glad to pronounce this is no longer an issue. Not!

14. Recommendations for care outpace the time available in primary care practice

Clinical question: How much time does it take for a primary care clinician to implement applicable guidelines for prevention and care in a typical practice?
Study design: Other
Setting: Primary care
Synopsis: These authors conducted a theoretical modeling study to estimate the time needed to provide all the preventive care, chronic care, and acute care according to current guidelines. To estimate the time burden on a typical primary care practice, they created 1000 hypothetical primary care panels of 2500 patients. They identified all the Grade A and Grade B preventive care guidelines for adults from the United States Preventive Services Task Force and the Advisory Committee on Immunization Practices of the Centers for Disease Control (N = 48). The authors picked guidelines for the top 10 chronic illnesses and calculated the average number and length of visits for acute illness among adults. They estimated the time with and without team-based care. The complete basket of services was estimated to require 26.7 hours per day, which includes 3.2 hours each day for documentation and inbox management, 14.1 hours for preventive care, 7.2 hours for chronic disease care, and 3.2 hours a day for acute care. Panel size affects work: Decreasing to a panel size of 1500 patients decreases physician time by 10.7 hours and increasing to 3000 patients increases time by 5.3 hours. Estimates for practices using high-functioning teams are lower: 9.3 hours per day of clinician time, which includes 2.6 hours per day for and inbox management. These estimates don't likely apply to countries with healthcare systems that aren't driven by insurance companies and their documentation requirements.
Bottom line: Well, it's good to know that a typical primary care clinician with a typical patient panel on a typical day can provide all necessary preventive care and acute and chronic illness care. Yeah, I'm kidding: The true estimate, if all boxes were ticked and all problems were completely addressed for all patients, is 26.7 hours a day, including 3.2 hours each day to care for and feed the electronic medical record monster. Using team-based care helps, but at an average 9.3 hours per day, don't expect to eat lunch or get home on time for dinner. Some pundits have asked guideline developers to consider the "time needed to treat" when formulating their advice.
Porter J, Boyd C, Skandari MR, Laiteerapong N. Revisiting the time needed to provide adult primary care. J Gen Intern Med 2023;38(1):147-155.

Final thoughts

To be a thoughtful and caring clinician requires balance and wisdom. Overzealous adherence to guidelines can overmedicalize the human experience. Aristotle described the virtue of ***phronesis*** or practical wisdom. Cosgrove and Shaughnessy argue that to become a phronimos (like our late colleague John Hickner) requires conscious attention to one's own practice through audit, feedback, judicious adherence to guidelines, and advocacy for people-as-patients at individual, community, and national levels.
Cosgrove L, Shaughnessy AF. Becoming a Phronimos: Evidence-Based Medicine, Clinical Decision Making, and the Role of Practical Wisdom in Primary Care. J Am Board Fam Med. Aug 9 2023;36(4):531-536. doi:10.3122/jabfm.2023.230034R1

Bottom Lines:

- Guidelines are fraught with problems including discordance among guidelines, conflict of interest, overly complicated recommendations, and limited applicability to primary care.
- Guidelines must explicitly state the level of evidence and strength of recommendation.
- Family physicians should read guidelines with skepticism and only implement those that follow explicit processes and that apply appropriately to primary care patients.

Depression and anxiety update — Kate Rowland, MD, MS

Objectives: At the end of this session, the participant will:

- Describe updates on the nonpharmacologic management of depression
- Prescribe appropriate medications for depression or anxiety, when indicated
- Identify appropriate nonpharmacologic therapies for anxiety

Every family physician and primary care clinician understands that depression and anxiety are highly prevalent conditions. The lifetime prevalence of major depression is around 20%- one in five of people in the US—and the lifetime prevalence of generalized anxiety is about 5%. The prevalence in symptoms, and the prevalence of these conditions in primary care is much higher. One study found about 20% of patients in a primary care office had a diagnosable anxiety disorder, and most of those were not treated.

Despite the high prevalence, and the known impact the symptoms will cause on the patient's life, anxiety and depression are relatively underrepresented in the medical literature. For both depression and anxiety, it is clear that some patients do better with medication, some with psychotherapy, and some with both, while some will improve with no treatment beyond supportive care. High-quality evidence on the best ways to distinguish a transient episode of situational depression from a chronic depression is lacking, as is evidence to help guide the best methods of identifying patients who benefit from medication therapy, and which medications to choose.

Terlizzi EP, Zablotsky B. Symptoms of anxiety and depression among adults: United States, 2019 and 2022. National health statistics reports. 2024 Nov 7(213):CS353885.

Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Annals of internal medicine. 2007 Mar 6;146(5):317-25.

Guidelines for treatment of depression

1. American College of Physicians guidelines for the treatment of acute depression in adults

Clinical question: What are the updated guidelines from the American College of Physicians for the treatment of acute depression?
Synopsis: This report updates the guidelines last issued by the American College of Physicians (ACP) in 2016. It is based on a separate systematic review that focused on patient-oriented outcomes; it specifically reviewed patient values and preferences. No guideline development members had conflicts of interest. The evidence was graded. For mild depression, the group recommends cognitive behavioral therapy (CBT) and not medication (conditional recommendation; low-certainty evidence). For moderate to severe symptom scores, the guidelines recommend, based on patient preference, either CBT or a second-generation antidepressant (i.e., not a tricyclic antidepressant) without recommending a specific one (strong recommendation; moderate-certainty evidence). The combination of psychotherapy and medication is also an option for moderate to severe depression (conditional recommendation; low-certainty evidence). Patients who don't respond to initial drug treatment should be switched to or augmented with CBT (conditional recommendation; low-certainty evidence), switched to a different medication, or treated with an additional antidepressant (conditional recommendation; low-certainty evidence).
Bottom line: For patients in the acute phase of major depressive disorder, the ACP continues the trend away from drug therapy and toward talk therapy. CBT is recommended as first-line treatment for patients with moderate symptoms (conditional recommendation). Citing evidence that up to 70% of patients with moderate to severe depression will not respond to a second-generation antidepressant, the group recommends offering CBT, medication therapy, or the combination of both to patients with more profound symptoms.
Overuse alert: This POEM aligns with the Canadian Psychiatric Association's Choosing Wisely Canada recommendation: Don't routinely use antidepressants as first-line treatment for mild or subsyndromal depressive symptoms in adults. Qaseem A, Owens DK, *Etxeandia-Ikobaltzeta I, et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: a living clinical guideline from the American College of Physicians. Ann Intern Med 2023;176(2):239-252.*

2. U.S. Veterans Affairs/Department of Defense guidelines on the treatment of major depressive disorder

Clinical question: How should major depressive disorder be treated, according to the U.S. Department of Veterans Affairs and Department of Defense guidelines?
Synopsis: The guideline working group comprised representatives from several disciplines and specialties. Patients were involved in focus groups to assess important aspects of treatment and to learn their values and preferences. There were no financial conflicts of interest. In a nod to the role of intellectual conflicts of interest, researchers were recused from discussion of evidence in the areas of their research. The recommendations were based on a systematic review of evidence. The guidelines continue to recommend screening of adults for depression and using a quantitative scale to monitor symptoms over time (both weak recommendations). These guidelines addressed uncomplicated depression, severe depression, and depression that has had a partial or limited response to

initial treatment. For uncomplicated depression, the authors suggest treating with either psychotherapy or pharmacotherapy alone (weak recommendation). They do not recommend a specific type of psychotherapy or whether it should be individually or in a group (weak recommendation). They do not give a recommendation for choice of drug therapy, other than to avoid nefazodone, monoamine oxidase inhibitors, and tricyclic antidepressants. Esketamine/ketamine should be reserved for patients who have not responded to several trials of pharmacotherapy. Patients with severe symptoms or with partial or limited response to treatment should be treated with a combination of psychotherapy and drug therapy.
Bottom line: New recommendations in these guidelines include monitoring patients with depression via an ongoing measurement tool and reserving ketamine/esketamine for patients who have not responded to several adequate trials of drug therapy. The recommendations do not prioritize either psychotherapy or drug therapy but suggest choosing a single approach for uncomplicated depression. You can find the full guidelines on the U.S. Department of Veterans Affairs website.
McQuaid JR, Buelt A, Capaldi V, et al. The management of major depressive disorder: synopsis of the 2022 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. Ann Intern Med 2022;175(10):1440-1451.

3. NICE guidelines for the treatment of depression

Clinical question: How should primary care physicians treat patients with symptoms of depression?
Study design: Practice guideline Setting: Various (guideline)
Synopsis: These guidelines are based on a systematic review of evidence conducted by a technical group. Mental health and primary care clinicians, along with lay members and administrators without financial conflicts of interest, made up the committee. They considered evidence of effectiveness, safety, cost, and availability, filling in with expert opinion when writing their recommendations. The guidelines recommend an assessment that "does not rely on symptom count . . . but also takes into account severity of symptoms, previous history, duration and course of illness." Functional impairment is also a part of the diagnosis. Treatment guidelines are different for first episodes of less severe and more severe depression; for both instances, the authors list options, including no treatment, in order of preference. For less severe depression, initial options include guided self-help and group cognitive behavioral therapy (CBT) or group behavioral activation (see graphic overview). For more severe depression, start with a combination of individual CBT with drug therapy, or CBT, individual behavioral activation, or antidepressant alone (see overview). Based on expert opinion, lithium and antipsychotics are offered for patients who do not respond to trials of the first-line options. To prevent relapse, the group suggests discussing continued treatment for people at low risk of recurrence. For patients at higher risk, they suggest either continuing the same treatment and dose or switching from medication therapy to psychological therapy or, if a combination of therapy is used, backing off to a single psychological or medication treatment. Bottom line: Refreshingly, these guidelines are labeled as information for not only health professionals, but also for people with depression, their families, and caregivers. The authors emphasize that, other than in the presence of suicidal ideation and intent, the diagnosis of depression is more than simply ticking boxes. They also highlight the primacy of an ongoing relationship between clinician and patient to make the diagnosis and to decide, together, on the best treatment. For less severe depression, guided self-help, group or individual therapies, or other nondrug treatments are first-line therapy; drug treatment comes in ninth of 11 options. CBT and drug treatment, together or alone, are starting points for the treatment of more severe depression. See the links in the synopsis for graphic overviews to guide shared decisions with your patients.
This POEM aligns with the Canadian Psychiatric Association's Choosing Wisely Canada recommendation: Don't routinely use antidepressants as first-line treatment for mild or subsyndromal depressive symptoms in adults.
Depression in adults: treatment and management. London: National Institute for Health and Care Excellence (NICE); 2022 Jun 29. www.nice.org.uk/guidance/ng222

Non-drug therapies for anxiety and depression

4. Exercise, especially resistance and mind-body exercise, improves depression scores in older adults

Clinical question: What types of exercise are effective in improving depression in older adults?
Study design: Meta-analysis (randomized controlled trials) Setting: Various (meta-analysis)
Synopsis: These authors searched several databases to identify randomized trials of various types of exercise in older adults with depression. Although the authors don't define the lower age of inclusion, the mean age for each the included studies exceeded 65 years. The authors pooled data on 5536 participants in 80 studies and conducted several analyses, including a network meta-analysis. Of the included studies, 23 were at high risk of bias; none were at low risk. Studies of exercise interventions have methodologic limitations, especially masking, so we are unlikely to see low risk studies, but more than 25% of these were at high risk of bias. Additionally, the authors found significant possibility of publication bias. Since the included studies used different scales for assessing depression severity, the authors report the standardized mean difference (SMD), where values between 0.2 and 0.5 are small effect sizes, values between 0.5 and 0.8 are medium effect sizes, and values higher than 0.8 are large effect sizes. Four types of exercise were used in the included studies: aerobic exercise, resistance exercise, mixed exercise, and mind-body exercise. After performing a bunch of statistical gymnastics, the authors report (based on the P scores with a range of 0 to 1, reflecting magnitude and precision of relative effects) the following order of effectiveness: resistance exercise (P = .957), mind-body exercise (P = .780), aerobic exercise (P = .442), and mixed exercise (P = .316). Overall, the SMDs reflected small to medium effects (range = 0.23 - 0.68). The authors found variable degrees of statistical heterogeneity among the data. They also estimated the metabolic equivalents (METs) for the interventions and, overall, found a U-shaped dose-response with the "sweet spot" at 760 METs (the minimum dose for effect was seen at 390 METs and the maximum dose for effect was seen at 1000 METs). For resistance exercise, the sweet spot was at 560 METs, and for mind-body exercise, it was 880 METs. Finally, as is common in many meta-analyses and network meta-analyses, the authors provide no data on adverse effects of the interventions.
Bottom line: In this network meta-analysis of low- to middling-quality studies, resistance exercise and mind-body exercise are moderately effective in improving the severity of depression in older adults.

Tian S, Liang Z, Tian M, et al. Comparative efficacy of various exercise types and doses for depression in older adults: a systematic review of paired, network and dose-response meta-analyses. Age Ageing 2024;53(10):afae211.

5. Consider formal exercise as initial therapy for patients with symptoms of depression

Clinical question: Is exercise an effective treatment for patients with symptoms of depression?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These authors conducted this network meta-analysis following PRISMA guidelines. They identified randomized trials with an exercise arm by searching 5 databases, including Cochrane CENTRAL, and found 218 studies (N = 14,170 participants) that included patients with mild to severe depression. Most of the studies were unmasked, which (combined with other bias risks) led the authors to judge the risk of bias to be high for almost 60% of the studies. There was no evidence of publication bias. Simple counseling on physical exercise or giving participants choice over the frequency, intensity, type, or time for exercise did not produce a clinically important benefit. However, many prescribed exercise interventions, from dance classes to walking/jogging, yoga, and strength training, produced a clinical benefit over another active treatment. Higher intensity of exercise was associated with greater benefit. There may be an expectancy bias (a type of placebo effect) that would explain the results.
Bottom line: Prescribing a specific exercise program, whether aerobic or strength training, produces a clinically meaningful result in patients with depression. The advice can't be simply to "exercise more" but should be a specific exercise prescription, just like a medication prescription, specifying the frequency, intensity, time (duration), and type of exercise.
Noetel M, Sanders T, Gallardo-Gómez D, et al. Effect of exercise for depression: Systematic review and network meta-analysis of randomised controlled trials. BMJ 2024;384:e075847.

6. Bright light therapy is effective for nonseasonal depressive disorders

Clinical question: Is bright light therapy effective treatment for adults with nonseasonal depressive disorders?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Unknown/not stated
Setting: Various (meta-analysis)
Synopsis These investigators thoroughly searched multiple databases, including MEDLINE, EMBASE, SCOPUS, Web of Science, PsychINFO, and the Cochrane Register, for English language–only randomized trials that compared bright light therapy (BLT) alone or BLT plus antidepressant with placebo, antidepressant monotherapy, or dim red light in adults with nonseasonal depression. BLT was defined as using a fluorescent light box that produces 10,000 lux white light for at least 30 minutes daily. Two individuals independently assessed individual trials for inclusion criteria and risk of bias using the Cochrane Risk of Bias tool. Disagreements were resolved by consensus discussion with a third reviewer. All 11 trials (N = 858 patients) that met inclusion criteria were scored at low risk of bias. Statistically significant higher remission and response rates occurred in the BLT group than in the non-BLT group (40.7% vs 23.5%, and 60.4% vs 38.6%, respectively). A subgroup analysis found a similar benefit to BLT for improving both remission and response rates in trials lasting less than 4 weeks and in trials lasting more than 4 weeks. Additional analyses found minimal heterogeneity among the individual trials and a low probability of publication bias.
Bottom line A previous review found moderate-quality evidence that supports the effectiveness of BLT for the treatment of nonseasonal depressive disorders. This updated meta-analysis of 11 individual trials published since 2000 found additional evidence to support the benefit of BLT as an effective treatment/adjunctive treatment for adults with nonseasonal depressive disorders.
Menegaz de Almeida A, Aquino de Moraes FC, Cavalcanti Souza ME, et al. Bright light therapy for nonseasonal depressive disorders. A systematic review and meta-analysis. JAMA Psychiatry 2025;82(1):38-46.

Novel treatments for depression: psychedelics

7. Among psychedelics, only psilocybin has demonstrated benefit to treat depression

Clinical question: Are psychedelic drugs effective for the treatment of depression?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These investigators searched 4 literature databases, including Cochrane CENTRAL, and 2 clinical trial databases. They identified 15 randomized controlled trials on psychedelics in a total of 811 adults with depressive symptoms. They also included 4 studies of escitalopram to use as an indirect comparison in this network meta-analysis. Two authors independently extracted the data and evaluated the research for risk of bias. Since psychedelics produce a rapid and noticeable effect, the investigators evaluated the issue of unmasking separately, finding that the placebo response was, surprisingly, less in the trials of psychedelics than in the studies of escitalopram. For the primary outcome — change in depression, measured by the Hamilton depression rating scale — high-dose psilocybin, which has the most research, was better than placebo and only slightly better (effect size 0.31) than escitalopram in patients with moderate to severe depression. Other psychedelics, including 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), and ayahuasca, were not more effective than placebo.
Bottom line: Now that research involving psychedelics is no longer verboten, psychedelic treatment is becoming the answer in search of a problem. Depression, it seems, is not one of the problems it can solve. Only high-dose psilocybin was more effective than placebo and perhaps slightly better, on average, than treatment with an antidepressant.
Hsu TW, Tsai CK, Kao YC, et al. Comparative oral monotherapy of psilocybin, lysergic acid diethylamide, 3,4-methylenedioxymethamphetamine, ayahuasca, and escitalopram for depressive symptoms: systematic review and Bayesian network meta-analysis. BMJ 2024;386:e078607.

Post-partum depression

8. Single postpartum dose of esketamine may reduce postpartum depression

Clinical question: In at-risk patients, does a single dose of esketamine reduce their likelihood of developing postpartum depression?
Study design: Randomized controlled trial (double-blinded)
Setting: Inpatient (any location)
Synopsis: These researchers enrolled 364 pregnant patients who presented for delivery and had mild or more severe depression identified at the time of admission (a median score of 10 of a possible 30 on the Edinburgh Postnatal Depression Scale). The participants were randomized, using concealed allocation, to receive either intravenous esketamine 0.2 mg/kg or saline placebo as a single dose immediately after delivery once the umbilical cord was clamped. By 42 days after birth, 6.7% of the women who received esketamine and 25.4% of the women who received placebo had a major depressive episode as diagnosed by the Mini-International Neuropsychiatric Interview (number needed to treat [NNT] = 6; 95% CI 4.6 - 7.6). Edinburgh Postnatal Depression Scale scores were lower at 7 and 42 days. Hamilton Rating Scale for Depression scores were lower at 42 days in the esketamine group, with 71.1% of these patients scoring in the “no depression” range as compared with 39% receiving placebo. Neuropsychiatric side effects, mainly dizziness, occurred in 33.5% of participants during or after receiving esketamine as compared with 11% of participants during or after receiving placebo (NNT = 5). I'm skeptical; given the high rate of depression in the placebo group, it is possible that part of the benefit might be due to a subject-expectancy effect, in which participants expected to be depressed unless they had some sort of strange experience after treatment (such as dizziness) that told them they'd been treated, which frequently happened with esketamine but not placebo.
Bottom line: Esketamine, given immediately after delivery to patients at risk for postpartum depression, seems to lessen the likelihood of depression as compared with placebo. Transient side effects are common.
Wang S, Deng C, Zeng Y, et al. Efficacy of a single low dose of esketamine after childbirth for mothers with symptoms of prenatal depression: randomised clinical trial. BMJ 2024;385:e078218.

Treatment-resistant depression

9. Esketamine is superior to quetiapine for remission of treatment-resistant depression

Clinical question: For patients with treatment-resistant depression, is an eskatamine nasal spray superior to the antipsychotic quetiapine?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (any)
Synopsis: In this trial, treatment-resistant depression was defined as a score of 34 or higher on an 84-point depression scale (higher is worse) and failure of 2 to 6 treatment regimens from at least 2 different drug classes with 25% or less reduction in symptoms. All patients were taking the maximally tolerated dose of a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor that was continued during the trial. At baseline, patients had a mean age of 45 years (range 18 to 74 years), 66% were women, and 39% had failed 3 or more treatments. The mean duration of the current episode of major depression was 66 weeks. Groups were balanced and allocation to groups was concealed. The trial was open label, but outcome assessors were masked to treatment assignment. The authors initially screened 811 participants in 27 countries, but after a 2-week run-in period, they only randomized 676 to either esketamine nasal spray or extended-release quetiapine. The initial single esketamine dose was 56 mg, increasing to up to 84 mg twice weekly, then weekly, and then weekly or every 2 weeks. Quetiapine was started at 50 mg with a maximum dose of 300 mg once daily. Patients were followed up for 32 weeks following randomization. The primary outcome was remission, defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) score of 10 or less at week 8 (range 0 to 60), and occurred more often in the esketamine group (27.1% vs 17.6%; P = .003, number needed to treat [NNT] = 11). Remission at week 32 was also more common with esketamine (49.1% vs 32.9%; P not reported; NNT = 7). Among those patients with remission at week 8, absence of relapse at week 32 was also more likely with esketamine (21.7% vs 14.1%; P < .05; NNT = 14). Serious treatment-related adverse events occurred for between 5% and 6% of patients in each group, although events leading to discontinuation of the medication were more common with quetiapine (11.0% vs 4.2%). Hospitalization for suicide attempt or worsening depression was uncommon and similar between groups.
Bottom line: Nasal esketamine spray is safe and somewhat more effective than extended-release quetiapine at inducing remission at 8 weeks (NNT = 10) and 32 weeks (NNT = 7) in patients with treatment-resistant depression.
Reif A, Bitter I, Buyze J, et al, for the ESCAPE-TRD Investigators. Esketamine nasal spray versus quetiapine for treatment-resistant depression. N Engl J Med 2023;389(14):1298-1309.

10. Single-dose psilocybin is beneficial in the short term for treatment-resistant depression

Clinical question: For patients with treatment-resistant depression, is a single dose of psilocybin effective at improving symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Psilocybin, a psychedelic compound found in some mushrooms, has been synthesized into a pharmaceutical-grade compound. These researchers identified adults who were experiencing an episode of treatment-resistant depression based on failure to respond to 2 to 4 adequate trials of antidepressants. At baseline, their mean age was 40 years, 52% were women, 92% were White, 86% had been experiencing their current episode for longer than 1 year, and all had moderate to severe depression based on the Hamilton Depression Scale. Groups were balanced at baseline and analysis was by modified intention to treat that included all patients with at least one outcome assessment. The 233 patients were randomized to receive either 1 mg, 10 mg, or 25 mg psilocybin in a single dose. The 1-mg group was considered unlikely to report any effect and was used as the control. The primary outcome was the change in the Montgomery–Åsberg Depression Rating Scale (MADRS), a 60-point scale where an improvement of at least 6 points would be considered clinically significant. At 3 weeks, the improvement in the MADRS score was 12 points in the 25-mg group, 7.9 points in the 10-mg group, and 5.4 points in the 1-mg group. The difference between the 25-mg group and the 1-mg group was clinically and statistically significant (-6.6 points; 95% CI -2.9 to -10.2). Remission, defined as a 50% reduction in the MADRS score, also

occurred significantly more often in the 25-mg group than the 1-mg group at 3 weeks (37% vs 18%; odds ratio [OR] 2.9; 1.2 - 6.6; number needed to treat [NNT] = 5). At 12 weeks, a sustained response was not seen significantly more often in the 25-mg group than in the 1-mg group (20% vs 10%; OR 2.2; 0.9 - 5.4). There were no statistically or clinically significant benefits seen in the 10-mg group compared with the 1-mg group. There were no important differences in severe adverse events among the groups, although nonsevere headache and nausea were more common in the 25-mg group.
Bottom line: At 3 weeks, a single 25-mg dose of psilocybin provided a clinically meaningful benefit for patients with treatment-resistant depression (NNT for remission = 5). However, the benefit was not well sustained at 12 weeks. Further study is needed to establish the optimal dose and frequency of treatment.
Goodwin GM, Aaronson ST, Alvarez O, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. N Engl J Med 2022;387(18):1637-1648.

11. Combination antidepressant therapy is more effective than monotherapy for acute severe depression and nonresponding depression

Clinical question: What is the treatment efficacy and tolerability of combination therapy compared with monotherapy for acute severe depression and recurrent depression in adults?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: The optimal management of an initial episode of acute severe depression and nonresponsive depression in adults remains uncertain. These investigators thoroughly searched, without language restrictions, multiple databases including MEDLINE, PsycINFO, Embase, and the Cochrane Central Register of Controlled Trials for randomized trials that compared antidepressant monotherapy with a combination of 2 antidepressants. Eligible trials included both first-line antidepressant treatment trials and trials that included patients resistant to improvement with initial therapy. In studies that included nonresponders, monotherapy (control group) patients received either continued monotherapy with the same antidepressant at the same or higher dose, or monotherapy with a different antidepressant. Two individuals independently evaluated individual trials for study eligibility and risk of bias using the Cochrane scoring tool. Disagreements were resolved by consensus agreement. The primary outcome was treatment efficacy measured as the standardized mean difference (SMD). Of the 39 individual trials, 15 were classified as "low risk of bias." Heterogeneity was minimal when restricted to studies with low risk of bias and an analysis for publication bias found minimal risk for altering the results.

Overall, combination therapy provided superior efficacy than monotherapy for both first-line treatment and among nonresponders (SMD 0.31; 95% CI 0.19 - 0.44). Results were similar when restricting the analyses to only studies with low risk of bias. The combination of a monoamine reuptake inhibitor with an antagonist of presynaptic alpha2-autoreceptors (ie, mirtazapine or trazodone) is associated with superior efficacy compared with monotherapy for both first-line treatment and for nonresponding patients. Combination therapy with bupropion was not associated with superior outcomes compared with monotherapy for first-line treatment, but was superior to monotherapy for nonresponding patients. Dropout rates due to adverse events were similar for both types of therapy.
Bottom line: This review found that combination therapy using a reuptake inhibitor (ie, a selective serotonin reuptake inhibitor, serotonin–noradrenaline reuptake inhibitor, or tricyclic antidepressant) with an antagonist of presynaptic alpha2-autoreceptors (mirtazapine or trazodone) is more effective than monotherapy for first-line treatment of acute severe depression and for those patients who are initially nonresponders to monotherapy. Dropout rates due to adverse events were similar for both combination therapy and monotherapy.
Henssler J, Alexander D, Schwarzer G, Bschor T, Baethge C. Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression. A systematic review and meta-analysis. JAMA Psychiatry 2022;79(4):300-312.

Anxiety updates

12. Long-term Outcomes of Cognitive Behavioral Therapy for Anxiety-Related Disorders: A Systematic Review and Meta-analysis

Importance: Cognitive behavioral therapy is recommended for anxiety-related disorders, but evidence for its long-term outcome is limited.
Objective: This systematic review and meta-analysis aimed to assess the long-term outcomes after cognitive behavioral therapy (compared with care as usual, relaxation, psychoeducation, pill placebo, supportive therapy, or waiting list) for anxiety disorders, posttraumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD).
Data sources: English-language publications were identified from PubMed, PsycINFO, Embase, Cochrane, OpenGrey (1980 to January 2019), and recent reviews. The search strategy included a combination of terms associated with anxiety disorders (eg, panic or phobi*) and study design (eg, clinical trial or randomized controlled trial).
Study selection: Randomized clinical trials on posttreatment and at least 1-month follow-up effects of cognitive behavioral therapy compared with control conditions among adults with generalized anxiety disorder, panic disorder with or without agoraphobia, social anxiety disorder, specific phobia, PTSD, or OCD.
Data extraction and synthesis: Researchers independently screened records, extracted statistics, and assessed study quality. Data were pooled using a random-effects model.
Main outcomes and measures: Hedges g was calculated for anxiety symptoms immediately after treatment and at 1 to 6 months, 6 to 12 months, and 12 months or more after treatment completion.
Results: Of 69 randomized clinical trials (4118 outpatients) that were mainly of low quality, cognitive behavioral therapy compared with control conditions was associated with improved outcomes after treatment completion and at 1 to 6 months and at 6 to 12 months of follow-up for a generalized anxiety disorder (Hedges g, 0.07-0.40), panic disorder with or without agoraphobia (Hedges g, 0.22-0.35), social anxiety disorder (Hedges g, 0.34-0.60), specific phobia (Hedges g, 0.49-0.72), PTSD (Hedges g, 0.59-0.72), and OCD (Hedges

g, 0.70-0.85). At a follow-up of 12 months or more, these associations were still significant for generalized anxiety disorder (Hedges g, 0.22; number of studies [k] = 10), social anxiety disorder (Hedges g, 0.42; k = 3), and PTSD (Hedges g, 0.84; k = 5), but not for panic disorder with or without agoraphobia (k = 5) and could not be calculated for specific phobia (k = 1) and OCD (k = 0). Relapse rates after 3 to 12 months were 0% to 14% but were reported in only 6 randomized clinical trials (predominantly for panic disorder with or without agoraphobia).
Conclusions and relevance: The findings of this meta-analysis suggest that cognitive behavioral therapy for anxiety-related disorders is associated with improved outcomes compared with control conditions until 12 months after treatment completion. At a follow-up of 12 months or more, effects were small to medium for generalized anxiety disorder and social anxiety disorder, large for PTSD, and not significant or not available for other disorders. High-quality randomized clinical trials with 12 months or more of follow-up and reported relapse rates are needed.
Van Dis EA, Van Veen SC, Hagenaars MA, et al. Long-term outcomes of cognitive behavioral therapy for anxiety-related disorders: a systematic review and meta-analysis. JAMA psychiatry. 2020 Mar 1;77(3):265-73.

13. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis

Background: Generalised anxiety disorder is a disease that can be associated with substantial dysfunction. Pharmacological treatment is often the first choice for clinicians because of the cost and resource constraints of psychological alternatives, but there is a paucity of comparative information for the multiple available drug choices.
Methods: A systematic review and network meta-analysis was performed on randomised trials in adult outpatients with generalised anxiety disorder identified from MEDLINE, Web of Science, Cochrane Library, ClinicalTrials.gov, Chinese National Knowledge Infrastructure (CNKI), Wanfang data, Drugs@FDA and commercial pharmaceutical registries. Placebo and active control trials were included. Data were extracted from all manuscripts and reports. Primary outcomes were efficacy (mean difference [MD] in change in Hamilton Anxiety Scale Score) and acceptability (study discontinuations for any cause). We estimated summary mean treatment differences and odds ratios using network meta-analyses with random effects. This study is registered with PROSPERO, number CRD42018087106.
Findings: Studies were published between Jan 1, 1994 and Aug 1, 2017, in which 1992 potential studies were screened for inclusion. This analysis is based on 89 trials, which included 25 441 patients randomly assigned to 22 different active drugs or placebo. Duloxetine (MD -3·13, 95% credible interval [CrI] -4·13 to -2·13), pregabalin (MD -2·79, 95% CrI -3·69 to -1·91), venlafaxine (MD -2·69, 95% CrI -3·50 to -1·89), and escitalopram (MD -2·45, 95% CrI -3·27 to -1·63) were more efficacious than placebo with relatively good acceptability. Mirtazapine, sertraline, fluoxetine, buspirone, and agomelatine were also found to be efficacious and well tolerated but these findings were limited by small sample sizes. Quetiapine (MD -3·60 95% CrI -4·83 to -2·39) had the largest effect on HAM-A but it was poorly tolerated (odds ratio 1·44, 95% CrI 1·16-1·80) when compared with placebo. Likewise, paroxetine and benzodiazepines were effective but also poorly tolerated when compared with placebo. Risk of reporting bias was considered low, and when possible all completed studies were included to avoid publication bias.
Interpretation: To our knowledge, this is the largest contemporary review of pharmacological agents for the treatment of generalised anxiety disorder by use of network analysis. There are several effective treatment choices for generalised anxiety disorder across classes of medication. The failure of initial pharmacological therapy might not be a reason to abandon a pharmacological treatment strategy. **Funding:** No funding was received for this research
Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. The Lancet. 2019 Feb 23;393(10173):768-77.

Bottom Lines:

- Recent guidelines are starting to emphasize accurate diagnosis of depression and first line talk therapy for non-severe depression.
- Effective non-drug options for depression include exercise and bright light therapy.
- High-dose psilocybin is slightly better than escitalopram for moderate to severe depression, but other psychedelics do not appear to be effective.
- Esketamine and psilocybin may be useful for treatment-resistant depression.
- Consider combination therapy for severe or non-responding depression.

Liver and lower gastrointestinal update — Kate Rowland, MD, MS

Objectives: At the end of this session, the participant will:
- Describe relevant primary care research updates in hepatology
- Explain new research regarding the management of irritable bowel syndrome
- Discuss updates in lower gastrointestinal disease management

These past few years have brought relatively few new studies about the lower GI tract- except a flood of new monoclonal antibodies for Crohn's. The other exception is a surprising emphasis on irritable bowel syndrome. Although, as we'll discuss, the quality of the evidence is not as high as we would always like, it's nice to have more attention paid to this common, chronic, and sometimes debilitating condition.

I was excited to dig into the literature around the treatment of metabolic-associated steatotic liver disease, or MASLD. I have been hearing a lot about the treatment of MASLD with GLP-1 agonists. Unfortunately the literature is so thin that there isn't enough to present. That's true right now, but may not be true for long- more GLP-1 studies are coming out all the time! Stay tuned.

Liver

1. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Background: Nonalcoholic steatohepatitis (NASH) is a progressive liver disease with no approved treatment. Resmetirom is an oral, liver-directed, thyroid hormone receptor beta-selective agonist in development for the treatment of NASH with liver fibrosis.
Methods: We are conducting an ongoing phase 3 trial involving adults with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3 (stages range from F0 [no fibrosis] to F4 [cirrhosis]). Patients were randomly assigned in a 1:1:1 ratio to receive once-daily resmetirom at a dose of 80 mg or 100 mg or placebo. The two primary end points at week 52 were NASH resolution (including a reduction in the nonalcoholic fatty liver disease [NAFLD] activity score by ≥2 points; scores range from 0 to 8, with higher scores indicating more severe disease) with no worsening of fibrosis, and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.
Results: Overall, 966 patients formed the primary analysis population (322 in the 80-mg resmetirom group, 323 in the 100-mg resmetirom group, and 321 in the placebo group). NASH resolution with no worsening of fibrosis was achieved in 25.9% of the patients in the 80-mg resmetirom group and 29.9% of those in the 100-mg resmetirom group, as compared with 9.7% of those in the placebo group (P<0.001 for both comparisons with placebo). Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was achieved in 24.2% of the patients in the 80-mg resmetirom group and 25.9% of those in the 100-mg resmetirom group, as compared with 14.2% of those in the placebo group (P<0.001 for both comparisons with placebo). The change in low-density lipoprotein cholesterol levels from baseline to week 24 was -13.6% in the 80-mg resmetirom group and -16.3% in the 100-mg resmetirom group, as compared with 0.1% in the placebo group (P<0.001 for both comparisons with placebo). Diarrhea and nausea were more frequent with resmetirom than with placebo. The incidence of serious adverse events was similar across trial groups: 10.9% in the 80-mg resmetirom group, 12.7% in the 100-mg resmetirom group, and 11.5% in the placebo group.
Conclusions: Both the 80-mg dose and the 100-mg dose of resmetirom were superior to placebo with respect to NASH resolution and improvement in liver fibrosis by at least one stage.
Harrison SA, Bedossa P, Guy CD, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. New England Journal of Medicine. 2024 Feb 8;390(6):497-509.

2. Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial

Objective To assess the efficacy and safety of the sodium-glucose cotransporter 2 inhibitor dapagliflozin in participants with metabolic dysfunction-associated steatohepatitis (MASH).
Design Multicentre, double blind, randomised, placebo controlled trial.
Setting Six tertiary hospitals in China from 23 November 2018 to 28 March 2023 Participants 154 adults with biopsy diagnosed MASH, with or without type 2 diabetes.
Interventions All participants were randomly assigned to receive 10 mg orally of dapagliflozin or matching placebo once daily for 48 weeks.
Main outcome measures The primary endpoint was MASH improvement (defined as a decrease of at least 2 points in non-alcoholic fatty liver disease activity score (NAS) or a NAS of ≤3 points) without worsening of liver fibrosis (defined as without increase of fibrosis stage) at 48 weeks. The secondary endpoints included the MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH. Analyses used the intention-to-treat dataset.
Results MASH improvement without worsening of fibrosis was reported in 53% (41/78) of participants in the dapagliflozin group and 30% (23/76) in the placebo group (risk ratio 1.73 (95% confidence interval (CI) 1.16 to 2.58); P=0.006). Mean difference of NAS was −1.39 (95% CI −1.99 to −0.79); P<0.001). MASH resolution without worsening of fibrosis occurred in 23% (18/78) of participants in the dapagliflozin group and 8% (6/76) in the placebo group (risk ratio 2.91 (95% CI 1.22 to 6.97); P=0.01). Fibrosis improvement without worsening of MASH was reported in 45% (35/78) of participants in the dapagliflozin group, as compared with 20% (15/76) in the

placebo group (risk ratio 2.25 (95% CI 1.35 to 3.75); P=0.001). The percentage of individuals who discontinued treatment because of adverse events was 1% (1/78) in the dapagliflozin group and 3% (2/76) in the placebo group.
Conclusion Treatment with dapagliflozin resulted in a higher proportion of participants with MASH improvement without worsening of fibrosis, as well as MASH resolution without worsening of fibrosis and fibrosis improvement without worsening of MASH, than with placebo.
Lin J, Huang Y, Xu B, Gu X, Huang J, Sun J, Jia L, He J, Huang C, Wei X, Chen J. Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial. BMJ. 2025 Jun 4;389.

Lower GI

3. Management of Patients With Acute Lower Gastrointestinal Bleeding: An Updated ACG Guideline

Acute lower gastrointestinal bleeding (LGIB) is a common reason for hospitalization in the United States and is associated with significant utilization of hospital resources, as well as considerable morbidity and mortality. These revised guidelines implement the Grading of Recommendations, Assessment, Development, and Evaluation methodology to propose recommendations for the use of risk stratification tools, thresholds for red blood cell transfusion, reversal agents for patients on anticoagulants, diagnostic testing including colonoscopy and computed tomography angiography (CTA), endoscopic therapeutic options, and management of antithrombotic medications after hospital discharge. Important changes since the previous iteration of this guideline include recommendations for the use of risk stratification tools to identify patients with LGIB at low risk of a hospital-based intervention, the role for reversal agents in patients with life-threatening LGIB on vitamin K antagonists and direct oral anticoagulants, the increasing role for CTA in patients with severe LGIB, and the management of patients who have a positive CTA. We recommend that most patients requiring inpatient colonoscopy undergo a nonurgent colonoscopy because performing an urgent colonoscopy within 24 hours of presentation has not been shown to improve important clinical outcomes such as rebleeding. Finally, we provide updated recommendations regarding resumption of antiplatelet and anticoagulant medications after cessation of LGIB.
Sengupta N, Feuerstein JD, Jairath V, Shergill AK, Strate LL, Wong RJ, Wan D. Management of patients with acute lower gastrointestinal bleeding: an updated ACG guideline. Official journal of the American College of Gastroenterology| ACG. 2023 Feb 1;118(2):208-31.

Recommendation Summary	SOR	Quality of Evidence
Recommend against antifibrinolytic agents (e.g., tranexamic acid).	Strong	Moderate
Recommend colonoscopy for most hospitalized LGIB patients.	Strong	Low
Patients with extravasation on CT angiography should be promptly referred for transcatheter arteriography/embolization. Colonoscopy may be considered in specialized centers.	Strong	Moderate
For hospitalized LGIB requiring colonoscopy, non-emergent inpatient colonoscopy is recommended. Urgent (<24 hours) colonoscopy does not improve outcomes.	Strong	Moderate
Treat diverticular stigmata of hemorrhage with through-the-scope clips, band ligation, or coagulation.	Strong	Moderate
Discontinue non-aspirin NSAIDs.	Strong	Low
Re-evaluate risks/benefits of non-aspirin antiplatelets in a multidisciplinary setting.	Strong	Low
Suggest discontinuing aspirin for primary prevention.	Conditional	Low
Suggest continuing aspirin for secondary prevention (established CVD).	Conditional	Low
Recommend resuming anticoagulation after LGIB cessation to decrease thromboembolism and mortality risks.	Strong	Moderate

Use risk stratification tools (e.g., Oakland score) to identify low-risk patients for early discharge and outpatient evaluation.	Conditional	Low
Use restrictive RBC transfusion strategy (threshold 7 g/dL) in hemodynamically stable patients.	Conditional	Low
Reversal suggested for life-threatening LGIB with substantially elevated INR. 4-factor PCC preferred over FFP.	Conditional	Very Low
Xa reversal ((idarucizumab, andexanet alfa) suggested for life-threatening LGIB unresponsive to initial resuscitation and drug cessation.	Conditional	Very Low
Colonoscopy may not be needed if bleeding has stopped and high-quality colonoscopy within 12 months shows diverticulosis without neoplasia.	Conditional	Very Low
CT angiography suggested as initial test for ongoing hemodynamically significant hematochezia. Low yield in minor LGIB or resolved bleeding.	Conditional	Low

Diagnostic tests

4. Ultrasound and CRP (rule out only) are the most useful tools for diagnosing acute diverticulitis that are feasible in primary care

Clinical question: What are the most accurate tests available in the primary care setting for diagnosing acute diverticulitis?
Study design: Meta-analysis (other)
Setting: Outpatient (primary care)
Synopsis: This meta-analysis identified 15 prospective and 2 retrospective studies of the diagnosis of acute diverticulitis using signs, symptoms, and tests that are feasible in the primary care setting. (None of the studies were done in the primary care setting.) Only 4 studies reported data regarding signs and symptoms, and the 2 studies that evaluated the same sign or symptom had very different sensitivity and specificity measures. Overall, the authors concluded that individual signs and symptoms are of uncertain value. A white blood cell count greater than 10 WBC/10^9 wasn't terribly helpful (positive likelihood ratio [LR+] 1.6, negative likelihood ratio [LR-] 0.56). Three studies reported C-reactive protein (CRP) greater than 10 mg/L and all reported excellent sensitivity (89% - 96%) but variable specificity. That means that a negative or normal CRP is helpful for ruling out acute diverticulitis, but an abnormal value is not terribly helpful (pooled sensitivity 93%, 95% CI 0.87 - 0.96; pooled LR- 0.17, 0.05 - 0.43). The most accurate test by far, and the one that is best studied, is ultrasound (sensitivity 92%; specificity 94%; LR+ 15.3; and LR- 0.08). Point-of-care ultrasound was as accurate as ultrasound in the radiology department.
Bottom line: Point-of-care ultrasound is increasingly finding a role at the bedside, and this study adds to that evidence base. In the patient with acute abdominal pain, point-of-care ultrasound has been shown to be highly accurate for diagnosis of appendicitis, small bowel obstruction, aneurysm — and now, acute diverticulitis.
Vijfschagt ND, de Boer MR, Berger MY, Burger H, Holtman GA. Accuracy of diagnostic tests for acute diverticulitis that are feasible in primary care: a systematic review and meta-analysis. Fam Pract 2024;41(1):1-8.

Irritable bowel syndrome (IBS) and functional abdominal disorders

5. Irritable bowel syndrome is associated with frequent antibiotic use

Clinical question: Is irritable bowel syndrome associated with antibiotic use?
Study design: Case-control
Setting: Population-based
Synopsis: This study, conducted in Sweden, used national databases to identify all cases of irritable bowel syndrome (IBS) over an 11-year period. All patients with IBS were matched with up to 5 control patients from the general population. Antibiotic use was quantified through a national prescription registry. Patients with IBS (29,111) were more likely than the 135,172 control patients to have received an antibiotic up to 1 year before diagnosis (74.9% vs 57.8%). After adjusting for demographics, healthcare use, and comorbidities, this translated into a 2.21-fold increased association between antibiotic use and IBS (95% CI 2.14 - 2.28). The risk of developing IBS increased with the number of courses of antibiotic treatment over the prior year; the rate was higher with 3 or more courses (odds ratio 3.36; 95% CI 3.24 - 3.49). This study did not account for antibiotic use that occurred as a result of hospitalization.
Bottom line: Presumably by perturbing the intestinal microbiome, antibiotic treatment is associated with an increase in the likelihood of the development of IBS; this is especially true with multiple courses of antibiotics. We have to remember that antibiotics are not magic bullets that home in precisely on a target but are more akin to buckshot that affects innocent (and useful) bystanders.
Staller K, Olén O, Söderling J, et al. Antibiotic use as a risk factor for irritable bowel syndrome: results from a nationwide, case-control study. Aliment Pharmacol Ther 2023;58(11-12):1175-1184.

6. British Society of Gastroenterology guidelines for the management of IBS

Clinical question: What is the best way to manage irritable bowel syndrome?
Synopsis: These guidelines from the British Society of Gastroenterology were created by a multidisciplinary panel that included primary care physicians, psychologists, dietitians, and gastroenterologists. Treatment recommendations were based on systematic reviews, and all other recommendations were based on a comprehensive review of the literature. There are dozens of recommendations; I'll outline the highlights. The guidelines advocate a pragmatic definition of irritable bowel syndrome (IBS) as at least 6 months of abdominal pain or discomfort, in association with altered bowel habits, in the absence of alarm signs or symptoms. Initial evaluation in primary care should include a complete blood count, C-reactive protein or sedimentation rate, and serology for celiac disease. For patients younger than 45 years who present with diarrhea, order a fecal calprotectin test to rule out inflammatory bowel disease. Screen for colorectal cancer in accordance with national guidelines; colonoscopy is only recommended for patients with alarm signs and symptoms or who are at increased risk for microscopic colitis (female, at least 50 years old, with comorbid autoimmune disease; weight loss; diarrhea for less than 12 months; or severe, nocturnal, or watery diarrhea). Consider testing for bile acid diarrhea in patients with nocturnal diarrhea or prior cholecystectomy. The guidelines recommend against testing for pancreatic insufficiency, small intestinal bacterial overgrowth, or carbohydrate intolerance if the symptoms are typical for IBS. First-line treatment recommendations include exercise and gradually increasing doses of soluble fiber (eg, ispaghula) but not insoluble fiber (eg, wheat bran). Consider probiotics, although the guideline doesn't recommend a specific species or dose. Consider loperamide for diarrheal symptoms; antispasmodics and peppermint oil for global symptoms, as well as abdominal pain and cramping; and polyethylene glycol for constipation. (Note that a recent POEM found no benefit to peppermint oil in a well-designed trial). Second-line drugs in primary care include tricyclic antidepressants and selective serotonin reuptake inhibitors. Other drug classes, such as medications targeting 5-HT-3 and 5-HT-4 receptors, should be prescribed after evaluation by a gastroenterologist.
Bottom line: This high-quality guideline provides sound advice for the evaluation and management of IBS in primary care.
Vasant DH, Paine PA, Black CJ, et al. British Society of Gastroenterology guidelines on the management of irritable bowel syndrome. Gut 2021;70(7):1214-1240.

7. Low FODMAPS diet is better than an oral spasmolytic for IBS (NNT = 7 – 9)

Clinical question: Which is more effective for the treatment of irritable bowel syndrome: an app to increase adherence to a low FODMAPS diet, or an oral antispasmodic agent (otilonium bromide)?
Synopsis: Both low FODMAPS diets and otilonium bromide (OB) have been shown in randomized trials to have efficacy for the treatment of irritable bowel syndrome (IBS). FODMAPS stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which are short-chain carbohydrates that are poorly absorbed by some people. This was a pragmatic trial, enrolling primary care patients given a diagnosis of IBS by their physician. Patients with psychiatric comorbidity, who had used a FODMAPS diet, or who had taken OB were excluded. The dietary intervention consisted of an app that provided guidance for a low FODMAPS diet and provided more than 100 recipes; the 40 mg OB intervention was given 3 times daily. Groups were similar at baseline, with a mean age of 41 years, and 76% were female. Analysis was by intention to treat. The primary outcome was a clinically significant improvement of 50 points on the 500-point IBS-Severity Symptom Scale. At 8 weeks, a response was noted by more patients in the FODMAPS group than in the OB group at 4 weeks (62% vs 51%; P = .02; number needed to treat [NNT] = 9) and at 8 weeks (71% vs 61%; P = .03; NNT = 10). The average decline in the score was also significantly higher in the FODMAPS group (-97 vs -77 points; P = .02). There were no differences between groups in overall quality-of-life scales. The authors also prespecified a subgroup analysis of the 309 patients (70%) who met the most recent Rome IV criteria for IBS. The benefit was greater in these patients in terms of the percentage of responders (77% vs 62%; P = .004; NNT = 7). Adherence was high and was actually better for the diet than for the medication (94% vs 73%).
Bottom line: This pragmatic trial found a clinically meaningful benefit of a low FODMAPS diet, implemented using an app, compared with an active medication comparator. Given its safety and low cost, the authors argue (and I agree) that a low FODMAPS diet should be first-line therapy for our patients with IBS. The process includes elimination of FODMAPS from the diet and then reintroducing foods, one at a time, until the offending food or foods are identified. The app used in this Belgian study was in French and Dutch, but there are many highly rated apps available. I found a free "Fast FODMAPS" app in the App store that included food lists, a food search, and other features. Caveat: These apps have not been evaluated in clinical trials.
Carbone F, Van den Houte K, Besard L, et al, for the Domino Study Collaborators. Diet or medication in primary care patients with IBS: the DOMINO study - a randomised trial supported by the Belgian Health Care Knowledge Centre (KCE Trials Programme) and the Rome Foundation Research Institute. Gut 2022;71(11):2226-2232.

8. Low FODMAP diet most likely to improve symptoms for patients with IBS

Clinical question: Is a low FODMAP diet effective for the treatment of irritable bowel syndrome?
Study design: Meta-analysis (randomized controlled trials) Synopsis: This was a network meta-analysis of 13 studies including 944 patients with irritable bowel syndrome (IBS). The studies were small (range: 30 to 110 patients), used the Rome III criteria to identify eligible patients, and compared a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) with usual diet, dietician advice, or the diet recommend by the British Dietetic Association (BDA). Nine trials were at low risk of bias across all domains other than double masking. Most studies enrolled patients with both IBS with constipation and IBS with diarrhea. The network meta-analysis combined direct and indirect comparisons and concluded that the low FODMAP diet was most likely to reduce pain, reduce bloating and distention, and improve bowel symptoms, and was also most likely to improve global IBS symptoms. The low FODMAP diet was superior to both the patient's usual diet and to the BDA recommended diet.
Bottom line: This network meta-analysis of the admittedly sparse literature concluded that compared with other diets, a low FODMAP diet (avoiding fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) is most likely to be effective for patients with IBS. With a low FODMAP diet, all offending foods are removed from the diet for 4 to 6 weeks, followed by a gradual and systematic reintroduction of foods to identify those that the patient can tolerate.
Black CJ, Staudacher HM, Ford AC. Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. Gut 2022;71(6):1117-1126.

9. Amitriptyline as second-line therapy improves symptoms in adults with IBS (ATLANTIS)

Clinical question: Does titrated low-dose amitriptyline improve symptoms in adults with irritable bowel syndrome who have failed first-line therapies?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care) Synopsis: These researchers recruited adults with irritable bowel syndrome (IBS) from primary care practices in the United Kingdom. To be included, the participants could have IBS of any subtype but had to have failed first-line treatments (diet, lifestyle, antispasmodics, laxatives, or antidiarrheals) and have at least moderate severity on the IBS Severity Scoring System (IBS-SSS). The researchers randomized the patients to receive titrated low-dose amitriptyline (n = 232) or matching placebo (n = 231). More than 80% of the participants had IBS with diarrhea (IBS-D) or with mixed diarrhea and constipation (IBS-M). The initial dose of amitriptyline was 10 mg every evening and the dose was increased over 3 weeks to a maximum of 30 mg. The researchers built in many overdose safeguards, such as assessing depression and suicidality and limiting the number of pills given to participants. Over the 6 months of the study, in addition to completing the IBS-SSS, the participants were asked “Have you had adequate relief of your IBS symptoms?” At the end of 6 months, a worrisome 23% discontinued their trial medication (20% of the amitriptyline-treated patients and 26% of placebo-treated patients) — the most common reason being adverse events. After 6 months, participants in both groups improved, but the amitriptyline-treated participants had a greater degree of improvement: 27 points better in their intention-to-treat analysis; the authors report, however, that 35 points is the minimum clinically important difference. More important, 61% of the amitriptyline-treated group reported meaningful improvement compared with 45% of those receiving placebo (number needed to treat = 7; 95% CI 4 - 16). These findings are consistent with guidelines from the American College of Gastroenterology and the British Society of Gastroenterology. The authors also provide a patient guide to self-titration of amitriptyline. Finally, this paper was recognized as a distinguished paper at the 2023 meeting of the North American Primary Care Research Group.
Bottom line: In this study, composed largely of adults with IBS-D and IBS-M with at least moderate severity despite first-line therapy, titrated low dose amitriptyline was more effective than placebo in improving symptoms.
Ford AC, et al, for ATLANTIS trialists. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;402(10414):1773-1785.

10. Enterosgel effective for irritable bowel syndrome with diarrhea (NNT = 8)

Clinical question: Is enterosgel safe and effective for the treatment of diarrhea-predominant irritable bowel syndrome?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Enterosgel (polymethylsiloxane polyhydrate) is an intestinal absorbent that is not pharmacologically active and is approved for over-the-counter purchase. The researchers identified adults, aged 16 to 75 years, who met the Rome IV criteria for diarrhea-predominant irritable bowel syndrome (IBS-D). Those with alarm symptoms or an abdominal pain score less than 2.5 or 3 were excluded. The 440 patients were randomized to receive enterosgel 15 g twice daily or matching placebo. After 5 days, the dose was gradually increased with a target dose of 30 g three times daily. There was an 8-week double-blind phase, followed by an 8-week open-label phase. Retention in the trial was good (421/440 in the double-blind phase), groups were balanced at baseline, and analysis was by intention to treat. Significantly more patients in the enterosgel group reported relief of symptoms, defined as at least a 30% decrease in abdominal pain and at least a 50% reduction in diarrheal stools, at 8 weeks (37.4% vs 24.3%; P = .002; number needed to treat = 8). The odds ratio for this outcome was 1.95 (95% CI 1.28 - 2.99). Significantly more patients in the enterosgel group also reported that their relief of symptoms was "adequate" at 4 weeks (56% vs 22%) and 8 weeks (69% vs 45%). Individual symptoms improved more and loperamide use was decreased more in the enterosgel group. Adverse events were similar and uncommon between groups. It is important to note that the study was funded by the maker of the product and most of the authors had significant conflicts of interest, including one who was CEO of the company.
Bottom line: Enterosgel appears to safely provide a moderate symptomatic benefit for persons with IBS-D. Its cost is $65 for a 3-pack of 225-g tubes on Amazon.com, which is approximately 11 days' worth at the most common study dose of 30 g twice daily. We don't know if it is better than other simple measures like fiber supplementation.
Howell CA, Kemppinen A, Allgar V, et al. Double-blinded randomised placebo controlled trial of enterosgel (polymethylsiloxane polyhydrate) for the treatment of IBS with diarrhoea (IBS-D). Gut 2022;71(12):2430-2438.

11. Some probiotic combinations may be effective for IBS symptoms

Clinical question: Is probiotic therapy effective to reduce symptoms in patients with irritable bowel syndrome?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: The authors assembled 82 studies including more than 10,000 patients by searching 3 databases (including Cochrane CENTRAL), conference proceedings, and bibliographies of eligible articles. Two investigators independently selected articles for inclusion (with no language restriction), extracted the data, and evaluated the studies for risk of bias. The authors included studies of many bacteria strains and combinations. There was substantial heterogeneity among the studies, which is not unexpected given the many bacteria studied, as well as the types of irritable bowel syndrome. Risk of bias was low for most studies, but so was evidence of benefit. For global symptoms, there was moderate certainty of a benefit of *Escherichia* strains, which may not be widely available. There was low certainty for *Lactobacillus* and *Bacillus* strains and for combinations. For abdominal pain or bloating/distention, there was low certainty of a benefit of individual strains or combinations of bacteria. Adverse effects were minimal across the studies.
Bottom line: People with irritable bowel syndrome can try various probiotic-containing products to lessen their symptoms, but on the whole, most people will not experience a significant reduction. Products containing *Escherichia* strains were the most likely to provide a benefit, but these are not widely available, at least in the United States.

Goodoory VC, Khasawneh M, Black CJ, Quigley EMM, Moayyedi P, Ford AC. Efficacy of probiotics in irritable bowel syndrome: systematic review and meta-analysis. Gastroenterology 2023;165(5):1206-1218.

12. Peppermint oil capsules might relieve symptoms of irritable bowel syndrome

Clinical question: Is peppermint oil more effective than placebo to decrease symptoms of irritable bowel syndrome?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These investigators identified 10 randomized controlled trials (N = 1030 participants) by searching 3 databases, including the Cochrane Registry, as well as a clinical trial database, conference proceedings, and reference lists of identified studies. The studies all had a duration of at least 4 weeks and compared peppermint oil with placebo in adults with irritable bowel syndrome (IBS). Two investigators independently selected, abstracted, and evaluated the studies. Most of the studies had some risk of bias and there was significant heterogeneity among the study results. All but one of the studies used capsules that delayed the release of peppermint oil into the small intestine or lower in the intestinal tract. Comparing improvement in the combination of global symptom scores and abdominal pain, there was a greater percentage of participants who responded to peppermint oil than placebo (45.7% vs 27.7%; number needed to treat = 4; 95% CI 3 - 11). When evaluating just high-quality studies, there was still more benefit with peppermint oil than placebo, though not as much. Side effects — gastroesophageal reflux, dyspepsia, and flatulence being most common — were higher in the peppermint group (number needed to treat to harm = 7; 6 - 205). The single small study that evaluated peppermint oil drops found a small benefit on reducing abdominal pain.
Bottom line: Based on low-quality research, peppermint oil, delivered by capsules that release it below the stomach, may be effective in improving symptoms of IBS. The single study that used peppermint oil drops found a benefit on abdominal pain, but that could also be caused by the placebo effect (due to the smell and taste). Peppermint oil was also associated with gastrointestinal symptoms, so it's not benign. Ingrosso MR, Ianiro G, Nee J, et al. Systematic review and meta-analysis: efficacy of peppermint oil in irritable bowel syndrome. Aliment Pharmacol Ther 2022 Sep;56(6):932-941.

13. Hypnosis for IBS

Clinical question: Is specific ("gut-directed") hypnotherapy effective in decreasing the symptoms of irritable bowel syndrome?
Study design: Randomized controlled trial (nonblinded)
Setting: Outpatient (specialty)
Synopsis: These investigators enrolled 119 participants with documented irritable bowel syndrome (per Rome III criteria) who did not respond to usual medical therapy. Patients were randomized (concealed allocation unknown) to receive either group or individual "gut-directed" hypnotherapy, delivered by an experienced nurse over 8 sessions using a published protocol. There was no placebo or usual care group. Most (92.5%) of the patients completed treatment, signaling a highly motivated cohort. A clinically relevant response, defined as at least a 50-point drop in a symptom scale ranging from 0 to 100, occurred in 69% of participants who received individual therapy and 57% of patients who received group-based therapy. Extracolonic symptoms, psychological symptoms, and quality of life also improved in both groups.
Bottom line: A specific, gut-directed series of hypnosis sessions, delivered either individually or in a group, decreased symptoms of irritable bowel syndrome in patients who previously had not responded to usual treatment. There was no placebo arm to assure us that the difference was not due to an expectancy effect.
Lövdahl J, Törnblom H, Ringström G, Palsson OS, Simrén M. Randomised clinical trial: individual versus group hypnotherapy for irritable bowel syndrome. Aliment Pharmacol Ther 2022;55(12):1501-1511.

14. Low-quality evidence: CBT and hypnosis may be effective for pain relief in children with functional abdominal pain

Clinical question: Which interventions are effective in decreasing pain in children with functional abdominal pain disorders?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These authors searched several databases and registries to identify published and unpublished randomized trials of psychosocial interventions for children with functional abdominal pain disorders. The studies had to enroll children 4 to 18 years of age with pain disorders diagnosed via explicit standardized diagnostic criteria. Ultimately, they included 33 trials with 2657 children (67% were girls). The follow-up ranged from 5 days to 4 months. The studies compared several different interventions with no intervention or with other therapies: cognitive behavioral therapy (CBT), educational support, different types of hypnotherapies, guided imagery, and relaxation. The following interventions were not capable of being meta-analyzed: different types of osteopathy, fiber intake, biofeedback, and journal keeping. Although the risk of bias tool evaluates several different domains, only one study was at low risk of bias for masking (since it used a sham control), and the remainder were of mixed risk of this and several other types of bias. Additionally, the authors found variability in outcome measures. Overall, they found that CBT was more likely than no intervention to “successfully treat” children (only 334 children; 38% vs 15%; number needed to treat [NNT] = 5; 95% CI 4 - 8) and to decrease pain frequency (446 children; standard mean difference [SMD] -0.36; modest effect) and pain intensity (332 children; SMD -0.58; modest effect). Additionally, hypnotherapy was more effective to “successfully treat” children (91 children; 56% vs 19%; NNT = 3; 2 - 6). However, it is unclear if CBT was more effective than educational support, if yoga was more effective than no intervention, or if any of the other previously mentioned interventions were effective. Finally, although the authors made great efforts to identify all the relevant studies, I suspect significant publication bias exists.
Bottom line: The existing data — from a small number of participants in studies with significant limitations — appear to show that CBT and hypnotherapy are modestly effective in decreasing pain in children with functional abdominal pain disorders.

Gordon M, Sinopoulou V, Tabbers M, et al. Psychosocial interventions for the treatment of functional abdominal pain disorders in children: a systematic review and meta-analysis. JAMA Pediatr 2022;176(6):560-568.

15. Placebo decreases pain in children with functional abdominal pain or IBS

Clinical question: Do open-label placebos decrease pain and medication use in children with functional abdominal pain or irritable bowel syndrome?
Study design: Cross-over trial (randomized)
Setting: Outpatient (specialty)
Synopsis: These researchers enrolled children, 8 to 18 years of age, with functional abdominal pain or irritable bowel syndrome (IBS) who were receiving care at 1 of 3 academic children's centers. At the initial visit, the children were introduced to the general concept of placebos and then they began 7 days of daily self-pain assessments using a 0- to 100-mm visual analog scale (VAS). The children with pain 25 mm or greater (n = 30) were then randomized to receive the control (symptom diary plus rescue analgesics) or the intervention (the placebo and additional details about the placebo). After 3 weeks the participants crossed over to the other group. After all the researchers' fancy analyses (crossover studies are analytically complex), 70% of the children reported higher pain scores during the control period (average VAS scores 45.0 vs 39.9). These differences are not, however, clinically significant. More noteworthy, 53% of the children took rescue analgesics during the control period compared with 6.7% during the placebo period. That translates to a number needed to treat of 3 (95% CI 2 - 5). **Bottom line:** In this small study, children with functional abdominal pain or IBS who knowingly took placebo had slightly lower pain scores and took less rescue medication.
Nurko S, Saps M, Kossowsky J, et al. Effect of open-label placebo on children and adolescents with functional abdominal pain or irritable bowel syndrome: a randomized clinical trial. JAMA Pediatr 2022;176(4):349-356.

Bottom Lines:

- Watch for new meds to treat MASLD
- POCUS plus CRP if you have it assess for diverticulitis, but a history and physical exam and CT will probably still be what most of us fall back on
- Antibiotics are associated with IBS. Some kinds of probiotics may help with symptoms.
- A low-FODMAPs diet can be helpful for IBS, as can some kinds of CAM therapies like hypnosis.

Objectives: At the end of this session, the participant will be able to:

- Describe thunderclap headaches and their serious underlying causes
- Summarize recent research on treating and preventing migraine headaches
- Summarize recent approaches to diagnosing and managing adults with Alzheimer's disease

Headache

The data from this first study are so jaw-dropping that we have to lead with it.

1. More than 70% of adults with thunderclap headache have serious diagnoses

Clinical question: How often are thunderclap headaches serious?
Study design: Cohort (retrospective)
Setting: Other
Synopsis: Thunderclap headaches, those that are sudden and maximally severe at onset, are scary and lead most adults to seek emergency care. These authors mined 10 years of electronic health record data at a single academic center to identify 932 adults with thunderclap headache who were seen in the emergency department, primary care department, or obtained a neurologist consultation (outpatient or inpatient). Of these, 393 (42.1%) had aneurysmal subarachnoid hemorrhage; some of these patients were referred from outside institutions. Of the remaining 539 adults, the authors report that 275 (51%) had serious findings: 97 (35.2%) had reversible cerebral vasoconstriction syndrome; 68 (24.7%) had nonaneurysmal subarachnoid hemorrhage; 27 (9.8%) had nontraumatic intracerebral hemorrhage; 22 (8.0%) had cerebral ischemia; and the rest had brain tumors, encephalopathy, meningitis, cerebral venous sinus thrombosis, or neurosurgical complications. Of those thought to have benign conditions, 102 (38.6%) had no abnormalities after evaluation. So, including those with aneurysmal subarachnoid hemorrhage, 71.7% of these patients had a serious condition.
Bottom line: In this study at an academic medical center, 71.7% of adults with thunderclap headaches had serious underlying diagnoses, most of which were identified with imaging.
Zorko Garbajs N, Nasr DM, Bellolio F, et al. Etiology and characteristics of non-aneurysmal thunderclap headache presenting to an acute setting. Am J Emerg Med 2024;85:217-224.

2. Ubrogepant during migraine prodrome is more effective than placebo to prevent moderate or severe headaches (NNT = 6)

Clinical question: Is ubrogepant (Ubrelvy) better than placebo in preventing headaches when taken during migraine prodrome?
Study design: Cross-over trial (randomized)
Setting: Outpatient (specialty)
Synopsis: These researchers recruited adults with at least one year of migraine, with or without aura, who had well-defined warning signs of an impending headache that were at least 75% accurate. These patients were asked to demonstrate this accuracy by keeping a 60-day headache diary. The researchers enrolled those patients who had 3 to 16 prodromal events with at least 75% accuracy in predicting a headache within 1 to 6 hours. This was a rather select group of participants: Of the 1087 who were initially assessed, 518 were randomized to receive 1 of 2 sequences to be taken during a prodrome. In sequence A, the participants took a placebo for the first prodromal episode and, after a 7-day washout period, took ubrogepant 100 mg during the second episode. In sequence B, the order was reversed. At the conclusion of the study, nearly 90% of the participants had at least one episode. The main outcome, the absence of a moderate to severe headache within 24 hours after taking the study drug, occurred in 28.6% of those taking placebo compared with 45.5% of those taking ubrogepant (number needed to treat [NNT] = 6; 95% CI 5 - 10). Although more participants taking ubrogepant than placebo experienced adverse effects (16.9% vs 11.9%; number needed to treat to harm [NNTH] = 21; 11 - 231), no participants discontinued their study medications because of adverse effects.
Bottom line: In this crossover study, patients whose migraine prodromes accurately predict the onset of headaches had fewer moderate to severe headaches if they took ubrogepant during the prodrome than if they took placebo. It is unclear whether this drug is any more effective than the much less expensive triptans, which can also be taken during the prodrome.
Dodick DW, Goadsby PJ, Schwedt TJ, et al. Ubrogepant for the treatment of migraine attacks during the prodrome: a phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. Lancet 2023;402(10419):2307-2316.

3. Triptans outperform older and newer treatments of acute migraine

Clinical question: Which type of treatment has a greater chance of relieving pain in patients with acute migraine?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These investigators searched 3 databases, as well as clinical trial registries and regulatory agencies and pharmaceutical company websites, to identify 137 randomized controlled trials comprising 89,445 adults treated for acute migraine. They excluded studies of patients who presented to an emergency department. Two researchers independently selected studies and extracted the data. They went the extra step and identified additional, unpublished data for 67% of the studies. From this wealth of information, the authors were able to perform a network meta-analysis of 17 medicines, ranging from analgesics to triptans. Using sumatriptan as the

standard, only eletriptan produces an average greater pain relief at 2 hours and decreased the use of rescue drugs in the first 2 to 24 hours. Triptans, as a group, are more effective than the newer treatments, including ubrogepant (Ubrelvy), lasmiditan (Reyvow), and rimegepant (Nurtec ODT, Vydura), as well as analgesics such as ibuprofen.
Bottom line: On average, triptans such as sumatriptan (Imitrex, Imigran, and others) and eletriptan (Relpax) are most likely to produce immediate relief of migraine pain and not require subsequent rescue medication.
Karlsson WK, Ostinelli EG, Zhuang ZA, et al. Comparative effects of drug interventions for the acute management of migraine episodes in adults: Systematic review and network meta-analysis. BMJ 2024;386:e080107.

4. Medications for preventing migraines in children and adolescents

Clinical question: What pharmacologic treatments are safe and effective for preventing migraine headaches in children and adolescents?
Study design: Systematic review
Setting: Various (meta-analysis)
Synopsis: A previous review reported minimal, if any, high-quality evidence that supports pharmacotherapy for preventing pediatric migraine. In this updated review, these investigators searched multiple databases — not including the Cochrane Registry of Clinical Trials — for additional randomized clinical trials that compared various pharmacotherapies head-to-head or with placebo for preventive therapy of migraine headache in children and adolescents younger than 18 years. Five individuals reviewed potential trials for eligibility and risk of bias using a standard validated scoring system. Disagreements were resolved after group consensus. A total of 45 individual trials (N = 3771) met inclusion criteria for the network meta-analysis. Individual studies had low to medium risk of bias. Pregabalin, topiramate with or without vitamin D, flunarizine, levetiracetam, riboflavin, cinnarizine, and amitriptyline were associated with reduced migraine frequency. Flunarizine and alpha-lipoic acid, flunarizine alone, pregabalin, and cinnarizine significantly attained a 50% or greater reduction in headache frequency and intensity from baseline compared with placebo. Propranolol and cinnarizine, pregabalin, valproate, levetiracetam, and cinnarizine significantly reduced migraine intensity. However, no treatments were associated with a significant reduction in disability or improved quality of life. Adverse events were highest with amitriptyline, topiramate, and valproate. No evidence supported a significant risk of publication bias.
Bottom line: This updated review found some evidence that supports multiple medications for reducing pediatric migraine headache frequency and intensity. However, no pharmacotherapy is associated with an overall improved quality of life or reduced attack duration.
Kohandel Gargari O, Aghajanian S, Togha M, et al. Preventive medications in pediatric migraine. A network meta-analysis. JAMA Network Open 2024;7(10):e2438666.

5. ACP guidline: Medications to prevent episodic migraines

DESCRIPTION: The American College of Physicians (ACP) developed this clinical guideline for clinicians caring for adults with episodic migraine headache (defined as 1 to 14 headache days per month) in outpatient settings. **METHODS:** ACP based these recommendations on systematic reviews of the comparative benefits and harms of pharmacologic treatments to prevent episodic migraine, patients' values and preferences, and economic evidence. ACP evaluated the comparative effectiveness of the following interventions: angiotensin-converting enzyme inhibitors (lisinopril), angiotensin II-receptor blockers (candesartan and telmisartan), antiseizure medications (valproate and topiramate), beta-blockers (metoprolol and propranolol), calcitonin gene-related peptide (CGRP) antagonist-gepants (atogepant or rimegepant), CGRP monoclonal antibodies (eptinezumab, erenumab, fremanezumab, or galcanezumab), selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors (fluoxetine and venlafaxine), and a tricyclic antidepressant (amitriptyline). ACP used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to analyze the effects of pharmacologic treatment on the following outcomes: migraine frequency and duration, number of days medication was taken for acute treatment of migraine, frequency of migraine-related emergency department visits, migraine-related disability, quality of life and physical functioning, and discontinuations due to adverse events. In addition, adverse events were captured through U.S. Food and Drug Administration medication labels and eligible studies. **RECOMMENDATIONS:** In this guideline, ACP makes recommendations for clinicians to initiate monotherapy for episodic migraine prevention in nonpregnant adults in the outpatient setting as well as alternative approaches if initial treatments are not tolerated or result in an inadequate response. All 3 ACP recommendations have conditional strength and low-certainty evidence. Clinical considerations provide additional context for physicians and other clinicians.
Qaseem A, Cooney TG, Etxeandia-Ikobaltzeta I, et al. Prevention of Episodic Migraine Headache Using Pharmacologic Treatments in Outpatient Settings: A Clinical Guideline From the ACP. Ann Intern Med. Feb 4 2025;doi:10.7326/ANNALS-24-01052

6. Erenumab injections for reducing nonopioid medication overuse headaches

Clinical question: Is erenumab effective in reducing headaches in adults with chronic migraines who also have nonopioid medication overuse headaches?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: This team of researchers, with a *long* list of industry ties, conducted a multinational multicenter phase 4 randomized trial of erenumab for treating adults (18 to 65 years of age) with chronic migraine who also have medication overuse headaches and have failed at least one preventive therapy. I suspect that this study will be used in an attempt to extend the patent by obtaining a new indication. The authors report that 1% to 2% of adults in the West have medication overuse headaches, so those who also have comorbid chronic migraine are unlikely to be seen in primary care settings. The study had 2 cohorts, one with opioid overuse headaches and one with nonopioid overuse headaches (the focus of this paper). The participants were randomized to receive erenumab 70 mg (n = 194), erenumab 140 mg (n = 194), or placebo (n = 194) administered as monthly injections for 24 weeks (Why do researchers insist on mixing time intervals? How many weeks are in a month?). During the study period, there was no requirement for detoxification and concomitant therapies were allowed. The authors don’t describe using intention to treat to analyze treatment

responses. They defined the main outcome — remission of medication overuse headache after 6 months — as having fewer than 10 headache days during months 4 to 6 of the study (which is really more of a reduction than a remission). Remission, using their definition, occurred in 52.6% of those receiving placebo, 60.3% of those receiving 70 mg erenumab (not statistically significant), and 69.1% of those receiving 140 mg erenumab (number needed to treat 7; 95% CI 4 - 15). Adverse events occurred with similar frequencies (66.2% of all participants) in each group. Similarly, adverse events leading to intervention discontinuation occurred in 1.5% of adults treated with placebo and 2.1% of adults treated with each of the erenumab doses.
Bottom line: In this industry-sponsored study, adults with chronic migraine and nonopioid medication overuse headaches who received monthly injections of 140 mg erenumab were more likely to achieve significant headache reductions at 6 months than those who received placebo. 70 mg erenumab was no more effective than placebo.
Tepper SJ, Dodick DW, Lanteri-Minet M, et al. Efficacy and safety of erenumab for nonopioid medication overuse headache in chronic migraine: a phase 4, randomized, placebo-controlled trial. JAMA Neurol 2024;81(11):1140-1149.

Dementia

In 2024, the Alzheimer's Association Workgroup released its new criteria for diagnosing Alzheimer's disease (www.ncbi.nlm.nih.gov/pubmed/38934362). The new criteria, in essence, make Alzheimer's disease a disorder of amyloid deposition ***regardless of current or future cognitive function.*** A recent commentary (www.ncbi.nlm.nih.gov/pubmed/38344833) pointed out that 1/3 of the workgroup members were paid by industry and another 1/3 had significant conflicts of interest. This is astounding, especially since the only extant study of amyloid-directed therapy in cognitively intact adults (www.ncbi.nlm.nih.gov/pubmed/37458272) demonstrated no meaningful benefit and trials of amyloid-directed therapy in adults with mild cognitive impairment or dementia have similarly found little to no benefit (Ebell et al; Ann Fam Med 2024; www.ncbi.nlm.nih.gov/pubmed/38253509). The prevalence of amyloid pathology among cognitively intact adults increases from 10% at age 50 to 44% at 90 years of age (www.ncbi.nlm.nih.gov/pubmed/25988462). That represents a lot of expense with little benefit. Like any good conspiracy, all you really need to do is, as Deep Throat told Woodward and Bernstein, follow the money. Fortunately, other groups are pushing back, as in this next paper.

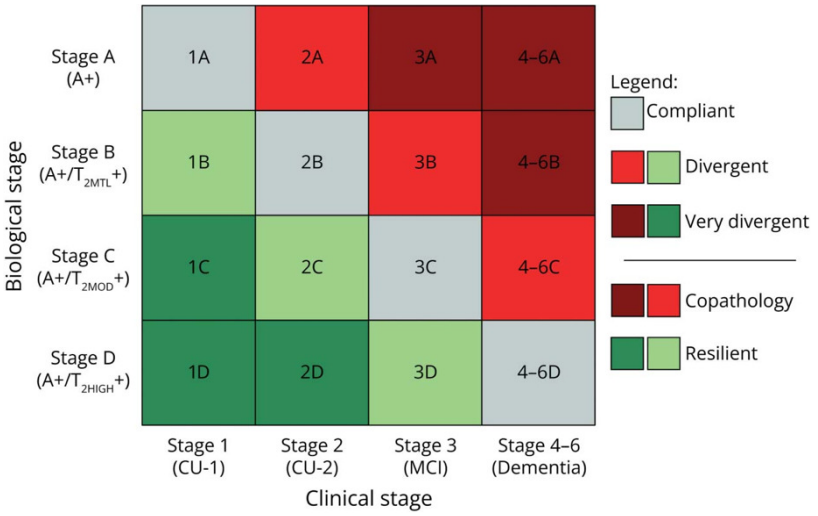
7. Working group response to updated Alzheimer's disease diagnostic criteria

IMPORTANCE: Since 2018, a movement has emerged to define Alzheimer disease (AD) as a purely biological entity based on biomarker findings. The recent revision of the Alzheimer's Association (AA) criteria for AD furthers this direction. However, concerns about a purely biological definition of AD being applied clinically, the understanding of AD by society at large, and the translation of blood-based biomarkers into clinical practice prompt these International Working Group (IWG) updated recommendations.
OBJECTIVE: To consider the revised AA criteria and to offer an alternative definitional view of AD as a clinical-biological construct for clinical use. The recommendations of the 2021 IWG diagnostic criteria are updated for further elaborating at-risk and presymptomatic states. **EVIDENCE REVIEW:** PubMed was searched for articles published between July 1, 2020, and March 1, 2024, using the terms "biomarker" OR "amyloid" OR "tau" OR "neurodegeneration" OR "preclinical" OR "CSF" OR "PET" OR "plasma" AND "Alzheimer's disease." The references of relevant articles were also searched. FINDINGS: In the new AA diagnostic criteria, AD can be defined clinically as encompassing cognitively normal people having a core 1 AD biomarker. However, recent literature shows that the majority of biomarker-positive cognitively normal individuals will not become symptomatic along a proximate timeline. In the clinical setting, disclosing a diagnosis of AD to cognitively normal people with only core 1 AD biomarkers represents the most problematic implication of a purely biological definition of the disease. **CONCLUSIONS AND RELEVANCE:** The ultimate aim of the field was to foster effective AD treatments, including preventing symptoms and dementia. The approach of diagnosing AD without a clinical and biological construct would be unwarranted and potentially concerning without a clear knowledge of when or whether symptoms will ever develop. It is recommended that those who are amyloid-positive only and, more generally, most biomarker-positive cognitively normal individuals, should not be labeled as having AD. Rather, they should be considered as being at risk for AD. The expansion of presymptomatic AD is viewed as a better diagnostic construct for those with a specific pattern of biomarkers, indicating that they are proximate to the expression of symptoms in the near future.
Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a Clinical-Biological Construct-An International Working Group Recommendation. JAMA Neurol. Dec 1 2024;81(12):1304-1311. doi:10.1001/jamaneurol.2024.3770

8. Real-world data don't support new Alzheimer's disease diagnostic criteria

Clinical question: How well do new Alzheimer's disease diagnostic criteria predict the outcomes of adults in a neuroimaging cohort?
Study design: Cross-sectional
Funding source: Foundation
Setting: Outpatient (specialty)
Synopsis: In 2024, a working group for the Alzheimer's Association re-defined Alzheimer's disease as a disorder of amyloid deposition independent of current or future cognition. As part of their report, they proposed a cascading model in which patients experience amyloid deposition followed by tau deposition, which leads to neurodegeneration and then cognitive impairment. Other guidelines still encourage the use of clinical criteria to diagnose Alzheimer's disease. In this current study, the authors adapted a 4x4 matrix based on

the amyloid cascade and on clinical stages of cognition (ranging from no impairment to dementia). In this matrix, a patient with no amyloid pathology would be expected to be cognitively intact, one with amyloid plus a little tau would be expected to have mild cognitive impairment, and so on. The authors applied this matrix to data from the Alzheimer's Disease Neuroimaging Initiative cohort in which 256 adults serially underwent magnetic resonance imaging, positron emission tomography, biomarker testing, and cognitive testing. The participants in this cohort were an average 73 years of age and 51% were female. The authors performed great feats of statistical gymnastics. Although the model performance varied based on the cutoff values for tau, the authors determined that between 31% and 36% of the cohort were concordant with the amyloid cascade. They also estimated that between 6% and 52% of those predicted to develop dementia did not. Between 17% and 63% of those at low risk of developing dementia based on the amyloid cascade actually developed it.



Bottom line: In this interesting analysis, new Alzheimer's disease diagnostic criteria and the amyloid cascade theory correctly predicts only one-third of adults who eventually develop dementia.
Mendes AJ, Ribaldi F, Pievani M, et al. Validating the amyloid cascade through the revised criteria of Alzheimer's Association Workgroup 2024 for Alzheimer disease. Neurology 2025;104(11):e213675.

9. Italian guideline on diagnosing and managing dementia and mild cognitive impairment

Clinical question: How should clinicians approach diagnosing and managing dementia or mild cognitive impairment in adults?
Study design: Practice guideline
Funding source: Government
Setting: Various (guideline)
Synopsis: The Italian Ministry of Health asked the Italian National Institute of Health to develop a guideline on the best approaches to diagnosing and managing dementia or mild cognitive impairment in adults. To do this, they convened a panel of 29 experts (from 17 healthcare professions) and 4 representatives of family members and caregivers. Although the label of "expert" was not clearly defined, 5 panelists were explicitly identified as having expertise in dementia and cognitive disorders. The full guideline with interactive tools and leaflets for patients and caregivers is available, as is a pdf of the English-language version without the tools and leaflets. I will attempt to summarize the key primary care–relevant recommendations. Perhaps the single most important recommendation is to involve the affected person in decision-making and to support caregivers throughout the entire course of the illness. The experts recommend that in primary care settings, clinicians should include medical history, physical examination, blood tests, and imaging to exclude potentially reversible or secondary causes of cognitive decline. They then recommend using validated cognitive tests and, if the results are abnormal, referral to a center with expertise in managing memory disorders. Additionally, clinicians should reassess persons with subjective cognitive decline whose cognitive test results are normal. Since anticholinergic drugs are associated with cognitive decline, the panel recommends monitoring their use (and considering alternatives). The guideline provides strategies for support of the patient and family, approaches for shared decision-making, advanced care planning, and communication. The panel made no clinical recommendations for screening or case finding; because of the paucity of evidence, these were included as recommendations for future research.
The panel recommends aerobic and nonaerobic exercise for persons with mild cognitive impairment and with mild and moderate dementia. The panel supports the use of music and art therapy but provides a long list of popular "treatments" and interventions that are ineffective, including ketogenic diets; aromatherapy; various "formulas," often containing omega-3 fatty acids, various vitamins, selenium, and so forth; ginseng, gingko biloba, and other herbal supplements; light therapy; acupuncture; laser therapy; and therapeutic robots. The panel recommends ***against*** using cholinesterase inhibitors, memantine, or monoclonal antibodies against amyloid for persons with mild cognitive impairment and has nuanced guidance for using cholinesterase inhibitors for adults with mild or moderate dementia. Finally, the panel also ***strongly*** recommends ***against*** using monoclonal antibodies against amyloid for persons with Alzheimer's disease.
Bottom line: This lengthy guideline provides *many* important recommendations relevant to primary care clinicians and their consultants — perhaps the most important of which is to keep the patient and family involved in the decision-making. The full online guideline includes many useful details and tools for clinicians who care for patients with cognitive decline.
Fabrizi E, Ancidoni A, Locuratolo N, et al, for the Guideline Working Group. The Italian guideline on diagnosis and treatment of dementia and mild cognitive impairment. Age Ageing 2024;53(11):afae250.

10. Amyloid-directed monoclonal antibodies provide no clinically meaningful cognitive benefits at the risk of clinically important harms

Clinical question: Are amyloid-directed monoclonal antibodies effective and safe in improving cognition in adults with mild cognitive impairment or Alzheimer disease?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Government

Synopsis: These researchers searched PubMed, Embase, and clinicaltrials.gov to identify high-quality (Jadad score > 3) phase III randomized trials with more than 200 participants that compared placebo with monoclonal antibodies against amyloid in adults with mild cognitive impairment or Alzheimer disease. Although they don't describe other efforts at identifying the gray literature, the authors graphically and statistically assessed the potential for publication bias. They report the potential for publication bias with the Clinical Dementia Rating Scale Sum of Boxes, which is one of the research scales that measures cognition, and they report that small studies that favored antibodies were potentially missing. Overall, the authors found that on various scales of cognition monoclonal antibodies were superior to placebo, but that the effect sizes were tiny and the data heterogeneous. While there was no difference in all-cause mortality, the antibodies caused more adverse events than placebo: amyloid imaging abnormalities (ARIA) with edema (16.6% vs 1.4%; number needed to treat to harm [NNTH] = 7) and with hemorrhage (18.4% vs 9.2%; NNTH = 10), and headaches (12.8% vs 9.9%; NNTH = 54). These findings are similar to another analysis published more than a year ago that was co-authored by 2 Essential Evidence Plus authors (https://pubmed.ncbi.nlm.nih.gov/38253509/).
Bottom line: This meta-analysis demonstrates (as do previous studies) that amyloid-directed monoclonal antibodies have tiny, clinically insignificant effects on various scales that measure cognition. These minimal "improvements" come at great physical and economic costs.
Tonegawa-Kuji R, Hou Y, Hu B, et al. Efficacy and safety of passive immunotherapies targeting amyloid beta in Alzheimer's disease: A systematic review and meta-analysis. PLoS Med 2025;22(3):e1004568.

Miscellaneous

11. Rate of new-onset seizures is less than 0.01% among SARS-CoV-2 vaccine recipients and placebo recipients

Clinical question: Do SARS-CoV-2 vaccines cause more new-onset seizures than placebo vaccines?
Study design: Meta-analysis (randomized controlled trials)
Setting: Various (meta-analysis)
Synopsis: These authors searched multiple databases, and the reference lists of review articles, editorials, and conference reports, and identified 6 randomized trials (118,440 participants) that reported new onset-seizures during the 28 days after vaccination against SARS-CoV-2 or with placebo or other vaccines. The studies had to confirm seizures either with a neurologist or with explicit criteria. Four studies enrolled only adults, 2 enrolled only children; all studies used placebo vaccines. All the studies were at low risk of bias. Among the studies, only 10 participants had a new-onset seizure (0.008%), 9 of whom received the active vaccine. This, however, was not statistically significant (odds ratio 2.70; 95% CI 0.76 - 9.57), most likely due to the rarity of the outcome. The authors detected no heterogeneity among the data ($I^2 = 0\%$). They also found no difference between mRNA vaccines (most widely used in the United States) and viral-vector vaccines. To assess the potential for poor or improper reporting of seizures, the authors also found that other neurologic events (eg, stroke, syncope, severe headache, and so forth) also occurred at similar rates between the groups. Finally, the authors found no evidence for publication bias and did not report on whether the study was powerful enough to detect meaningful differences.
Bottom line: In this meta-analysis, the overall rate of new-onset seizures is quite low. Although there was no statistically significant difference between vaccinated and placebo groups, this study lacks power to be certain.
Rafati A, Jameie M, Amanollahi M, et al. Association of new-onset seizures with SARS-CoV-2 Vaccines: A systematic review and meta-analysis of randomized clinical trials. JAMA Neurol 2024;81(6):611-618.

12. Limited data show anticonvulsants are associated with a small reduction in early seizures in adults with mild or moderate traumatic brain injury

Clinical question: Do anticonvulsants prevent seizures during the first 7 days in adults with mild or moderate traumatic brain injury?
Study design: Meta-analysis (other)
Setting: Various (meta-analysis)
Synopsis: These authors searched several databases to identify studies in which adults with mild or moderate traumatic brain injuries received anticonvulsants to prevent seizures in the first 7 days following injury. To limit potential sources of heterogeneity, they only included studies in which the patients received care from a trauma center in a high-income country. The authors had hoped to analyze individual patient–level data but were unable to obtain these. Ultimately, they included 8 studies (N = 5637) that reported seizure rates for patients with mild or moderate traumatic brain injuries, 5 of which reported separate data for mild injuries. Because of the rarity of early seizures, the authors reasonably reported the overall absolute risk reduction (ARR) and the ARR for individual studies. All but 2 of the studies were retrospective; none were randomized trials. All were rated as having good methodologic quality, but keep in mind that even good-quality retrospective studies cannot overcome biases such as channeling effects and confounding and tend to overestimate the true effects of therapeutic interventions. The most widely used anticonvulsants were levetiracetam, phenytoin, and valproic acid. In the studies, the rate of post-traumatic seizures ranged from 0% to 4%. The overall ARR was 0.6% (95% CI 0.1% - 1.2%). For patients with mild injuries, the ARR was also 0.6% (0.01% - 1.2%). The authors found very little heterogeneity in these data and little evidence of publication bias. Although they don't report data on the harms of therapy, the authors raise concerns that the small benefit could be offset by adverse effects and by the inappropriate use of anticonvulsants beyond 7 days.
Bottom line: In this well-done analysis, the authors found limited data on the use of anticonvulsants following mild or moderate traumatic brain injuries. The included studies found a low rate of seizures and a small benefit that would need to be balanced against potential (and unreported) harms.
Pease M, Mittal A, Merkaj S, et al. Early seizure prophylaxis in mild and moderate traumatic brain injury: A systematic review and meta-analysis. JAMA Neurol 2024;81(5):507-514.

13. Botox is effective for essential or isolated head tremor (NNT = 3 - 5)

Clinical question: Are 2 injections of botulinum toxin type A (Botox), 12 weeks apart, effective for the treatment of essential or isolated head tremor?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (specialty)
Synopsis: Medical treatments that are somewhat effective for essential hand tremor are less effective or ineffective for head tremor. These French researchers identified 117 patients at 17 centers with an essential or isolated head tremor that was moderately troublesome or worse. Patients with a diagnosis of Parkinson disease or a cerebellar syndrome were excluded, as were those with cervical dystonia. At baseline, the mean age of participants was 65 years, 80% were women, and all but 7% were White. Patients were randomized to receive injections of Botox or 0.9% saline placebo at baseline and at 12 weeks and were then followed up for a total of 24 weeks. The initial dose was 75 IU and was injected into splenius capitis muscle under electromyographic guidance; the dose could be increased to 100 IU if the 6-week assessment showed no response. To ensure masking, syringes were wrapped in foil prior to injection. Groups were balanced at baseline and analysis was by intention to treat; both patients and researchers were masked to treatment assignment. The primary outcome was the patient's assessment of the severity of their tremor using the Clinical Global Improvement (CGI) scale at 18 weeks. It ranged from 3 to -3, where 3 is very much improved, 2 is much improved, 1 is minimally improved, 0 is no change, and negative values correspond to worsening of tremor. At 18 weeks (6 weeks after the second injection), a good response, defined as a score of 2 or 3 on the CGI scale, occurred more often in the Botox group (31% vs 9%; P = .009, number needed to treat [NNT] = 5). A similar rate of good clinical response was seen at 6 weeks after the initial injection (44% vs 7%; relative risk [RR] 6.0; 95% CI 2.2 - 16.0; NNT = 3) but not at 24 weeks (23% vs 13%; RR 1.8; 0.77 - 4.1). Headache, neck pain, stiffness, and dysphagia (in 10%) were more common in the Botox group but were generally mild and transient. One patient in the Botox group was hospitalized for severe dysphagia, and another was hospitalized for a complaint of weakness, dizziness, and confusion.
Bottom line: In patients with an essential or isolated head tremor, 2 injections of Botox bilaterally into the splenius capitis muscle provides a good clinical response at 6 weeks after the second injection (NNT = 5), but the response wanes at 12 weeks. Side effects were usually mild and transient, but one patient was hospitalized for severe dysphagia.
Marques A, Pereira B, Simonetta-Moreau M, et al, for the Btx-HT Study Group. Trial of botulinum toxin for isolated or essential head tremor. N Engl J Med 2023;389(19):1753-1765.

Bottom Lines:

- Thunderclap headaches are serious business
- Ubrogepant during migraine prodrome prevents moderate or severe headaches (but so do triptans)
- Triptans are the most effective drugs for acute migraine abortive therapy
- Cognitively intact adults who are amyloid-positive should not be labeled as having Alzheimer's disease but should be considered as being at risk for AD.
- Medications should not be used in adults with mild cognitive impairment

Complementary and alternative medicine Kate Rowland, MD, MS

Objectives: At the end of this session, the participant will:

- Describe updates to the complementary and alternative medicine literature
- Explain the uses and limitations of complementary and alternative for common conditions
- Employ point of care resources relevant to complementary and alternative therapies

Depending on how they are defined, somewhere between 25 and 50% of people in the US employ complementary and alternative therapies to treat or prevent disease. An expansive definition of CAM includes the use of multivitamins, which are used by more than half of the US population for general health, while more targeted CAM therapies, such as herbal therapies, was reported by about 17% in a national survey.

Patients with more chronic conditions used CAM therapies, including both vitamins, supplements, and other therapies, compared with healthier patients. This held true for mind-body therapies, mindfulness, chiropractic therapy, and massage therapy as well. Patients with multiple chronic conditions were also more likely to use more than one CAM therapy compared with patients without chronic conditions.

In other words, patients we see in primary care are very likely to use CAM therapies, regardless of whether they disclose their use to us. It's worthwhile to know what patients are doing to better inform our advice.

Falci L, Shi Z, Greenlee H. Multiple chronic conditions and use of complementary and alternative medicine among US adults: results from the 2012 National Health Interview Survey. Preventing chronic disease. 2016 May 5;13:E61.

Patient expectations from CAM therapies

1. Yoga intervention for colorectal cancer survivors: a qualitative study exploring participants' expectations and experiences.

Introduction: Colorectal cancer (CRC) survivors often struggle with side effects following treatment such as reduced quality of life, fatigue and psychological distress and need therefore efficient comprehensive interventions. The aim of this qualitative study was to explore CRC survivors' expectations before the yoga intervention as well as their unique experiences beyond those reported with standard questionnaires.
Methods: Interpretative phenomenological approach was used in this qualitative study. Semi-structured interviews were conducted before and after a 10-week yoga program (90 min once a week, Hatha Yoga) with CRC survivors enrolled in a randomized controlled trial. Thematic analysis was used to uncover themes present in participants' accounts.
Results: Nine patients participated in the interviews, mean interview duration was 27.49 min (SD = 7.71) before and 38.41 min (SD = 15.93) after the intervention. Our analysis identified following themes: (1) representations and expectations from the yoga intervention; (2) course structure and implementation; (3) perceptions and effects of the intervention; (4) differences between the study yoga intervention and other physical activities. The superordinate theme regarding effects of intervention included aspects of intervention at multiple levels such as emotional, physical, behavioral and spiritual.
Conclusions: This qualitative study provides valuable insight regarding CRC survivors' expectations and experiences following a 10-week yoga intervention. While expectations varied from skepticism to specific symptom improvement, the majority of participants had a positive, open attitude towards yoga. Consistent with participants' experiences, yoga may represent a promising intervention for CRC survivors if the groups' specific concerns are taken into account.
Bilc MI, Pollmann N, Eisenmann C, et al. Yoga intervention for colorectal cancer survivors: a qualitative study exploring participants' expectations and experiences. Annals of Medicine. 2024 Dec 31;56(1):2397571.

Women's health

2. An "evidence map" for menopause. What complementary and alternative medicine practices have been studied to treat genitourinary symptoms of menopause?

These researchers searched 3 databases (but not Cochrane CENTRAL) to identify 57 English-language studies of 39 nonhormonal interventions for vulvovaginal, urinary, and sexual symptoms associated with menopause. Too bad they limited the studies to those published in English, since studies of natural products often are published in German and other languages. The modalities include mind and body practices — such as mindfulness, yoga, and acupuncture — and natural products ranging from phytoestrogens to Lactobacillus to oral and vaginal vitamins. Oddly, this is a "state of the literature" and not an analysis of what interventions are effective. Even odder, they consider sexual education, lifestyle interventions, and cognitive behavioral therapy to be either complementary or alternative (I'm not sure which). I'm not sure what to do with this information. This large research project only reports on which complementary and alternative medicine modalities are used to treat genitourinary symptoms of menopause; it doesn't enlighten us by telling us which ones work.
Ullman KE, Diem S, Forte ML, et al. Complementary and alternative therapies for genitourinary syndrome of menopause: An evidence map. Ann Intern Med 2024;177(10):1389-1399.

3. The Effect of Yoga Therapy in Premenstrual Syndrome: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

Objective: Up to 80% of women of reproductive age are thought to experience premenstrual stress, which is characterised by physical, psychological, and behavioural changes. Yoga activity lowers harmful inflammatory secretions that provide comfort for premenstrual syndrome (PMS) sufferers.
Data sources: The following worldwide databases were searched for this systematic review: Scopus, PubMed, Cochrane Library, PEDro, and Google Scholar from inception to August 2022.
Study selection: A population, intervention, comparison, outcome, and study design framework was used for searching. Population included those with PMS or premenstrual tension syndromes, the intervention included yoga therapy, comparator was with control group, and outcome measures included blood pressure (BP) (systolic BP [SBP], diastolic BP [DBP]) and heart rate (HR).
Data extraction and synthesis: To evaluate the study, we employed the methodological index for randomised controlled trials. Fixed effects meta-analysis and qualitative synthesis were conducted. A total of 14 studies out of 224 were included. The main outcome measures included in this review were SBP, DBP, HR, and Moos Menstrual Distress Questionnaire. For the meta-analysis, 7 studies were considered. Three studies contributed data of SBP (mean difference [MD] -0.30; 95% CI -2.29 to 1.69, heterogenicity [I^2] = 96%, P = 0.00001) and DBP (MD -0.25; 95% CI -0.99 to 0.49, I^2 = 79%, P = 0.009). HR results from 4 studies were included (MD 0.08; 95% CI -0.83 to 0.99, I^2 = 89%, P = 0.00001). A total of 3 studies contributed data of Moos Menstrual Distress Questionnaire (MD 1.50; 95% CI 0.91-2.10, I^2 = 92%, P = 0.00001).
Conclusion: Yoga can help people with both medical and psychological conditions including menstrual pain, irregular periods, stress, tension, and anxiety. It has been shown to lessen women's emotional, behavioural, and physical PMS symptoms, which has enhanced their quality of life.
Ranga M, Dev K. The Effect of Yoga Therapy in Premenstrual Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of Obstetrics and Gynaecology Canada. 2024 Jun 12:102579.

Older adults

4. Neither mindfulness training nor exercise improve memory or executive function

Clinical question: Does mindfulness training, exercise, or both improve cognitive function in older adults who have subjective cognitive concerns but no dementia?
Study design: Randomized controlled trial (double-blinded) **Setting:** Population-based
Synopsis: The health benefits of mindfulness meditation have been enthusiastically communicated by national speakers and workshops for decades. These investigators identified 585 community-dwelling adults, aged 65 to 84 years, who responded positively to questions about whether they or others had noticed trouble with their memory. Eligible participants showed no cognitive impairment consistent with dementia on a standardized scoring tool. Study participants randomly received assignment (allocation concealed) to 1 of 4 intervention groups: (1) Mindfulness-based stress reduction (MBSR) alone, (2) exercise alone, (3) combined MBSR and exercise, or (4) health education (control). All interventions occurred for 18 months. The MBSR intervention consisted of 8 weekly 2.5-hour classes plus a half-day retreat on MBSR meditation practices and enhancement exercises, followed by 12 months of maintenance once-per-month MBSR classes. The exercise intervention consisted of facility-based, instructor-supervised 1.5-hour classes twice weekly for 6 months, followed by once-per-week classes for the 12-month maintenance period. Exercise sessions focused on aerobics, resistance training, and functional exercises with the goal of at least 300 minutes per week. The health education intervention consisted of classes with the same time commitment as the MBSR intervention but without any specific goals other than general information on living with chronic health conditions. Individuals who assessed outcomes remained masked to treatment group assignments. The primary outcomes were episodic memory and executive function assessed using previously validated scoring tools. Follow-up occurred for 93% of participants at 18 months. Using intention-to-treat analysis, no significant group differences occurred for either of the primary outcomes at 6 months or 18 months. Physical performance, including aerobic fitness and strength, as well as sleep quality significantly improved with exercise. MBSR did not significantly influence any independent variables, including self-reported mindfulness.
Bottom line: This study found no benefit of MBSR training, exercise, or a combination of both for improving cognitive function in older adults with subjective cognitive concerns but no dementia. Physical performance, including aerobic fitness and strength, as well as sleep quality significantly improved with exercise. MBSR did not significantly influence any independent variables, including self-reported mindfulness.
Lenze EJ, Voegtle M, Miller JP, et al. Effects of mindfulness training and exercise on cognitive function in older adults. A randomized clinical trial. JAMA 2022;328(22):2218-2229.

5. Meds, music, and massage to treat anxiety in residents of long-term care facilities

Clinical question: What pharmacologic and nonpharmacologic measures are effective in managing anxiety in residents of long-term care facilities?
Study design: Meta-analysis (randomized controlled trials) **Setting:** Nursing home/extended care facility
Synopsis: These authors systematically searched several databases, registries, and the gray literature* to identify randomized trials of therapies to reduce anxiety in persons who reside in long-term care facilities. They followed high-quality methodologic procedures and translated foreign language publications to allow for data extraction. Although they identified 80 eligible trials, only 10 were suitable for pooling of data. None of the studies were at low risk of bias. The studies ranged in size from 11 to 659 participants; most had fewer than 100 participants. The interventions were wide-ranging: medications, music, touch, multicomponent therapies, exercise or movement, robotic animals or therapy dolls, education, psychotherapy, cognitive behavioral therapy, reminiscence, and “other.” The comparison interventions included usual care, social interaction, another active intervention, and placebo. While all the studies included anxiety assessments, anxiety was the primary outcome in only 15 studies. The authors did not pool data for the 9 trials of pharmacologic interventions but found that antipsychotics and anxiolytics were more effective than their comparators in reducing

anxiety. In the comparisons that allowed for pooling, the authors report medium to large effect sizes: music versus usual care (standardized mean difference [SMD] -0.82), music versus social interaction (SMD -0.41), and massage versus usual care (SMD -4.32). The authors found significant heterogeneity among these data. Finally, while the authors report that the nonpharmacologic therapies are low risk, they did not actually report any data on harms.
* Gray literature refers to unpublished studies, not studies of the elderly.
Bottom line: The data on managing anxiety in residents of long-term care facilities are limited to poor-quality studies but suggest that medications, music, and massage are effective.
Atchison K, Watt JA, Ewert D, Toohey AM, Ismail Z, Goodarzi Z. Non-pharmacologic and pharmacologic treatments for anxiety in long-term care: a systematic review and meta-analysis. Age Ageing 2022;51(9):afac195.

6. Is the addition of oral Chinese herbs to donepezil effective in improving cognition in adults with mild cognitive impairment?

Study design: Meta-analysis (randomized controlled trials) **Setting:** Various (meta-analysis)
Synopsis: These researchers combed multiple databases and registries and the reference lists of published systematic reviews to identify randomized trials that evaluated oral Chinese herbs added to donepezil to treat adults with mild cognitive impairment (MCI). The authors excluded studies of single compounds extracted from certain herbs, such as gingko biloba, because the authors claim these are "not classified as traditional Chinese herbal medicines." Ultimately, they included 20 studies (1611 participants), all of which took place in China and lasted from 1 month to 6 months. Eleven studies reported adverse event rates. The included studies used 81 Chinese herbs in 16 different formulations. The authors report that all studies had concerns about their risk of bias. Overall, compared with control patients, participants who used Chinese herbs had an average 1.88-point improvement (95% CI 1.52 - 2.24; I2 = 41%) of their Mini-Mental State Examination score and a 2.01-point improvement (1.57 - 2.44; I2 = 52%) on the Montreal Cognitive Assessment. The minimum clinically important difference is 1 to 2 for the Mini-Mental State Examination and 1 for the Montreal Cognitive Assessment. The authors report that the rate of adverse events, mainly gastrointestinal, was similar for control patients and herb-treated participants (overall 9.8%). Although the authors report no graphic or statistical evidence for publication bias, they only found 20 studies, so these assessments are not terribly robust.
Bottom line: This meta-analysis of short-term, small, low-quality studies found that adding traditional oral Chinese herbs to donepezil improves cognitive function in adults with MCI. A recent Italian guideline recommends against using cholinesterase inhibitors and other remedies in these patients. The natural history of untreated MCI is variable. An American Academy of Neurology guideline reported that 14% to 38% of adults with mild cognitive impairment revert to normal cognition. Although MCI is worrisome to patients and their families and caregivers, the data on the effectiveness and safety of pharmacologic interventions and herbal medicines are such that other interventions, such as exercise, music, and cognitive stimulation, should be recommended. Interested readers should refer to the original article for further details of the included herbal medicines.
Liu L, Zhang CS, Zhang AL, Cai Y, Xue CC. Oral Chinese herbal medicine combined with donepezil for mild cognitive impairment: A systematic review and meta-analysis. J Am Geriatr Soc 2024;72(12):3890-3902.

7. Can a cognitively enhanced tai chi program improve cognition and walking in older adults with mild cognitive impairment?

Study design: Randomized controlled trial (single-blinded) **Setting:** Outpatient (any)
Synopsis: These investigators enrolled 318 community-dwelling adults at least 65 years of age (mean age 76 years) with self-reported memory decline or concern, but without a clinical diagnosis of dementia, and a Clinical Dementia Rating global score of 0.5 or lower. The participants were assigned, using concealed allocation, to 1 of 3 interventions: (1) standard tai chi; (2) cognitively enhanced tai chi; or (3) a stretching program. Cognitively enhanced tai chi comprised learning the form while being asked to concurrently complete mildly challenging cognitive tasks, such as repeating numbers or ignoring deliberate miscuing by the instructor, which is sort of the opposite of the meditative goal of tai chi. All participants completed a 60-minute exercise session twice weekly for 24 weeks, delivered to their home via Zoom. On average, participants who received cognitively enhanced tai chi outperformed patients who received tai chi alone or stretching on the 30-point Montreal Cognitive Assessment (by 1.5 points and 2.8 points, respectively), which persisted at the 48-week follow-up. Participants in the tai chi alone and enhanced tai chi groups performed significantly better than participants in the stretching group on dual-task walking, which is an assessment of walking gait while performing cognitive tasks that is negatively affected by mild cognitive impairment. These results may not be widely applicable; the participants were almost all (96%) White, a majority were college graduates who did not live alone, and, of course, they all had the wherewithal to use Zoom.
Bottom line: Older, White, college-educated people with mild cognitive impairment benefited from 6 months of twice-weekly online classes of tai chi (tai ji quan) training that was interwoven with mildly challenging cognitive tasks ("cognitively enhanced tai chi") as compared with participants who received tai chi training alone or stretching exercises.
Li F, Harmer P, Eckstrom E, Fitzgerald K, Winters-Stone K. Clinical effectiveness of cognitively enhanced tai ji quan training on global cognition and dual-task performance during walking in older adults with mild cognitive impairment or self-reported memory concerns: a randomized controlled trial. Ann Intern Med 2023;176(11):1498-1507.

Musculoskeletal care

8. Is acupuncture effective for patients with chronic sciatica from herniated disk?

Study design: Randomized controlled trial (single-blinded)
Funding source: Government **Setting:** Outpatient (any)
Synopsis: These investigators enrolled 216 participants (68% were female; average age 51.3 years) with unilateral sciatica from herniated disk for more than 3 months, with moderate to severe leg pain (an average 60 out of a possible 100). The participants were

randomized, using concealed allocation, to receive acupuncture or sham acupuncture (needles inserted at non-acupoints) for 30 minutes for 10 sessions over 4 weeks. More than one-third of the participants previously had experienced acupuncture. At the end of treatment, pain scores decreased an average of 31 points in the acupuncture group and an average 15 points in the sham group (P < .001). A 15-point or greater difference in pain reduction is considered to be clinically relevant. Scores on the Oswestry Disability Index decreased an average 13 points in the treatment group versus 5 points in the control group (a difference of 7 or greater is clinically relevant). Treatment benefit began in the second week of treatment and was still significant at 52 weeks. Participants were masked to which treatment they received and only guessed their treatment assignment correctly approximately half the time.
Bottom line: Four weeks of acupuncture was better than sham acupuncture to decrease pain and disability associated with chronic sciatica, lasting at least 11 months after 1 month of treatment. (LOE = 1b)
Tu JF, Shi GX, Yan SY, et al. Acupuncture vs sham acupuncture for chronic sciatica from herniated disk: A randomized clinical trial. JAMA Intern Med 2024;184(12):1417-1424.

9. Mindfulness-based intervention is effective for chronic pain when delivered virtually

Clinical question: Is mindfulness-based treatment effective to decrease disability associated with chronic pain when delivered via video to groups or individuals?
Study design: Randomized controlled trial (single-blinded)
Setting: Outpatient (any) Synopsis: This study enrolled 811 US armed forces veterans who had chronic pain, defined as having pain of at least 4 on a scale of 0 to 10 lasting at least 6 months, usually due to extremity pain/arthritis or back pain. Although 63% of participants were given at least one mental illness diagnosis, the authors excluded patients with severe depression, psychotic symptoms, and poorly controlled bipolar disorder. The participants were randomized, using concealed allocation, to receive a mindfulness-based intervention, in group or self-paced sessions, delivered via videoconference or to receive usual care. The group-based format comprised 8 weekly 90-minute sessions of prerecorded educational and instructional videos presented by a certified mindfulness instructor, combined with workbook reflections and facilitated group discussions. The self-paced program comprised the same content delivered in eight 30- to 60-minute weekly sessions viewed by participants on their own, with 3 phone calls with a facilitator to discuss progress, plans for practice, and strategies to address challenges. The third group did not receive any additional intervention. Pain-related function interference, measured by the Brief Pain Inventory interference scale, was significantly lower for both group and individual mindfulness training than for usual care at 10 weeks, 6 months, and 1 year. The probability of a 30% improvement on the scale as compared with the control group was greater at 10 weeks and 6 months for group treatment, and at all 3 time points for self-paced mindfulness training.
Bottom line: Mindfulness training, delivered via pre-recorded, weekly videos, is effective to decrease loss of function in patients with chronic pain. Delivering the videos in groups was no more effective than having individuals watch the videos on their own, though both methods involved having trained facilitators reach out to participants; that is, they were not just given a website and told to get started.
Burgess DJ, Calvert C, Hagel Campbell EM, et al. Telehealth mindfulness-based interventions for chronic pain: the LAMP randomized clinical trial. JAMA Intern Med 2024;184(10):1163-1173. Erratum in JAMA Intern Med 2024;184(10):1270.

10. Acupuncture in the emergency department adds to musculoskeletal pain relief

Clinical question: Does either auricular or peripheral acupuncture provide additional short-term pain relief of acute musculoskeletal pain when added to usual care?
Study design: Randomized controlled trial (nonblinded)
Setting: Emergency department
Synopsis: This study enrolled 236 adults who presented to an emergency department with acute onset musculoskeletal pain of the neck, back, arms, or legs. The participants were randomized, using concealed allocation, to receive 20 to 30 minutes of either auricular ("battlefield") acupuncture or peripheral acupuncture to various body sites at the discretion of the acupuncturist; a third (control) group received evaluation by the acupuncturist but did not receive acupuncture. Battlefield acupuncture, which uses up to 5 short dart-like needles sequentially placed at ear sites until pain relief occurs, has been used not only by armed services but also to treat various painful conditions or procedures. All patients also received usual care, which consisted of oral analgesia or ice or heat treatment administered in the waiting room after the initial assessment. Using a 10-point rating scale, pain scores at 1 hour after treatment decreased (from an average of 7) by an average 2.1 (95% CI 0.7 - 2.6) with auricular acupuncture and 1.6 (0.3 - 2.1) with peripheral acupuncture, as compared with a decrease of 0.5 with usual care alone (P < .001; no difference between acupuncture methods). Both acupuncture methods produced a clinically important difference (ie, a change of at least 1.3). Average satisfaction scores with acupuncture were 4.4 out of a possible 5 on a Likert-type scale. A sham acupuncture group would have been helpful to separate out a placebo effect. Long-term pain relief and satisfaction were not studied.
Bottom line: Auricular (battlefield) acupuncture and peripheral acupuncture are both effective when added to analgesia for acute musculoskeletal pain treatment in an emergency setting to further reduce pain.
Eucker SA, et al, for the Duke Emergency Department Acupuncture Research team. An adaptive pragmatic randomized controlled trial of emergency department acupuncture for acute musculoskeletal pain management. Ann Emerg Med 2024;84(4):337-350.

Mental health

11. Frequent acupuncture may reduce opioid cravings and methadone dose in patients with opioid use disorder

Clinical question: Can acupuncture treatment reduce methadone dosing and reduce opioid craving in patients with opioid use disorder?
Study design: Randomized controlled trial (double-blinded) **Setting:** Outpatient (specialty)

Synopsis: These investigators enrolled 118 patients who were receiving methadone to manage opioid use disorder. The patients were an average of 48 years of age, had taken an opioid for an average of 14 years, were receiving an average dose of 42 mg methadone daily for at least 6 weeks, and had opioid craving scores of 80 to 84 of a possible 100 (although 100% of participants had negative opioid urine screens). The participants were randomized, using concealed allocation, to receive either acupuncture or sham acupuncture at the Dingshen-zhen, Sishen-zhen, and Shouzhi-zhen acupoints, which are sites most often used to treat psychiatric disorders. Treatments were 3 times a week for 8 weeks for 30 minutes per session. Acupuncturists were not masked, but everyone else involved in the study, including patients, data collectors, nurses, and physicians, was masked. At the end of treatment, 62% of treated participants had decreased their methadone dose by at least 20% compared with 29% in the sham treatment group (number needed to treat = 3; 95% CI 2 - 8). Opioid craving scores decreased an average of 16 points with treatment versus 4.4 with placebo (P < .001). The baseline opioid craving scores in this study were high, which makes me wonder how long the participants had been taking methadone or if they were not treated with high enough doses (60 mg - 120 mg is usually the effective dose).
Bottom line: Twenty-four sessions of acupuncture over 8 weeks reduces methadone dosing and opioid cravings in patients who are being managed for long-term opioid use disorder.
Lu L, Chen C, Chen Y, et al. Effect of acupuncture for methadone reduction: a randomized clinical trial. Ann Intern Med 2024;177(8):1039-1047.

12. Electroacupuncture is effective for insomnia treatment in adults with depression

Clinical question: Is electroacupuncture effective for the treatment of insomnia in adults with depression?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: These investigators identified adults, aged 18 to 70 years, who met standard international criteria for both depression and insomnia/poor quality of sleep. Eligible participants (N = 270) randomly received (concealed) assignment to 1 of 3 treatment groups: (1) electroacupuncture (EA) for 30 minutes 3 times per week for 8 consecutive weeks; (2) sham acupuncture (SA; a pricking sensation without insertion) on the same schedule as EA; or (3) the standard advice on exercising regularly, eating healthfully, and managing stress. Study participants in the EA and SA groups wore eye masks during their treatment sessions and served as their own judicial assessors of subsequent sleep quality and quality of life. Complete follow-up occurred for 91.5% of participants at 32 weeks. Using intention-to-treat analysis, patients in the EA group reported significantly lower insomnia severity scores than the SA and control groups during the 8-week treatment and the 24-week follow-up periods (-4.7; 95% CI -5.4 to -3.9 and -5.0; -5.8 to -4.1, respectively). Similarly, patients in the EA group reported significantly lower depression scores using the 17-item Hamilton Depression Rating Scale (-5.5; -6.8 to -4.3, with lower scores indicating improving depressive symptoms) than the SA group (-5.8; -6.8 to - 4.7) and the control group (-8.8; -10.1 to -7.4). Patients in the EA group also reported significantly improved self-rated anxiety scores compared with the SA and control groups. No significant group differences occurred with adverse events. Approximately 62% of patients in the SA group guessed incorrectly about their group assignment after study completion.
Bottom line: This study found that EA is more effective than SA or usual care for improving insomnia symptoms in adults with depression.
Yin X, Li W, Liang T, et al. Effect of electroacupuncture on insomnia in patients with depression. A randomized clinical trial. JAMA Network Open 2022;5(7):e2220563.

13. Music therapy for autistic people

Background Social interaction and social communication are among the central areas of difficulty for autistic people. Music therapy uses music experiences and the relationships that develop through them to enable communication and expression, thus attempting to address some of the core problems of autistic people. Music therapy has been applied in autism since the early 1950s, but its availability to autistic individuals varies across countries and settings. The application of music therapy requires specialised academic and clinical training which enables therapists to tailor the intervention to the specific needs of the individual. The present version of this review on music therapy for autistic people is an update of the previous Cochrane review update published in 2014 (following the original Cochrane review published in 2006).
Objectives To review the effects of music therapy, or music therapy added to standard care, for autistic people.
Search methods In August 2021, we searched CENTRAL, MEDLINE, Embase, eleven other databases and two trials registers. We also ran citation searches, checked reference lists, and contacted study authors to identify additional studies.
Selection criteria All randomised controlled trials (RCTs), quasi-randomised trials and controlled clinical trials comparing music therapy (or music therapy alongside standard care) to 'placebo' therapy, no treatment, or standard care for people with a diagnosis of autism spectrum disorder were considered for inclusion.
Data collection and analysis We used standard Cochrane methodological procedures. Four authors independently selected studies and extracted data from all included studies. We synthesised the results of included studies in meta-analyses. Four authors independently assessed risk of bias (RoB) of each included study using the original RoB tool as well as the certainty of evidence using GRADE.
Main results We included 16 new studies in this update which brought the total number of included studies to 26 (1165 participants). These studies examined the short- and medium-term effect of music therapy (intervention duration: three days to eight months) for autistic people in individual or group settings. More than half of the studies were conducted in North America or Asia. Twenty-one studies included children aged from two to 12 years. Five studies included children and adolescents, and/or young adults. Severity levels, language skills, and cognition were widely variable across studies. Measured immediately post-intervention, music therapy compared with 'placebo' therapy or standard care was more likely to positively effect global improvement (risk ratio (RR) 1.22, 95% confidence interval (CI) 1.06 to 1.40; 8 studies, 583 participants; moderate-certainty evidence; number needed to treat for an additional beneficial outcome (NNTB) = 11 for low-risk population, 95% CI 6 to 39; NNTB = 6 for high-risk population, 95% CI 3 to 21) and to slightly increase quality of life (SMD 0.28, 95% CI 0.06 to 0.49; 3 RCTs, 340 participants; moderate-certainty evidence, small to medium

effect size). In addition, music therapy probably results in a large reduction in total autism symptom severity (SMD −0.83, 95% CI −1.41 to −0.24; 9 studies, 575 participants; moderate-certainty evidence). No clear evidence of a difference between music therapy and comparison groups at immediately post-intervention was found for social interaction (SMD 0.26, 95% CI −0.05 to 0.57, 12 studies, 603 participants; low-certainty evidence); non-verbal communication (SMD 0.26, 95% CI −0.03 to 0.55; 7 RCTs, 192 participants; low-certainty evidence); and verbal communication (SMD 0.30, 95% CI −0.18 to 0.78; 8 studies, 276 participants; very low-certainty evidence). Two studies investigated adverse events with one (36 participants) reporting no adverse events; the other study found no differences between music therapy and standard care immediately post-intervention (RR 1.52, 95% CI 0.39 to 5.94; 1 study, 290 participants; moderate-certainty evidence).

Authors' conclusions The findings of this updated review provide evidence that music therapy is probably associated with an increased chance of global improvement for autistic people, likely helps them to improve total autism severity and quality of life, and probably does not increase adverse events immediately after the intervention. The certainty of the evidence was rated as 'moderate' for these four outcomes, meaning that we are moderately confident in the effect estimate. No clear evidence of a difference was found for social interaction, non-verbal communication, and verbal communication measured immediately post-intervention. For these outcomes, the certainty of the evidence was rated as 'low' or 'very low', meaning that the true effect may be substantially different from these results. Compared with earlier versions of this review, the new studies included in this update helped to increase the certainty and applicability of this review's findings through larger sample sizes, extended age groups, longer periods of intervention and inclusion of follow-up assessments, and by predominantly using validated scales measuring generalised behaviour (i.e. behaviour outside of the therapy context). This new evidence is important for autistic individuals and their families as well as for policymakers, service providers and clinicians, to help in decisions around the types and amount of intervention that should be provided and in the planning of resources. The applicability of the findings is still limited to the age groups included in the studies, and no direct conclusions can be drawn about music therapy in autistic individuals above the young adult age. More research using rigorous designs, relevant outcome measures, and longer-term follow-up periods is needed to corroborate these findings and to examine whether the effects of music therapy are enduring.

Geretsegger M, Fusar-Poli L, Elefant C, Mössler KA, Vitale G, Gold C. Music therapy for autistic people. Cochrane Database of Systematic Reviews. 2022(5).

Bottom Lines:

- Patients may not be expecting the moon, but are often open to improvement with CAM.
- Exercise is good for many things but does not improve cognition in older adults with mild cognitive impairment. Maybe try Chinese herbs or tai chi.
- Acupuncture should be done well by someone trained to do it; it can be useful for some MSK and mental health conditions
- Music may be good for anxiety among older adults and symptoms in people with autism

Top 20 POEMs of 2024 **Henry C. Barry, MD, MS**

Objectives: At the end of this session, the participant will be able to:

- Discuss the top 20 research studies for primary care.
- Discuss how these research studies have potential to change practice.
- Discuss POEMs consistent with the principles of the Choosing Wisely campaign

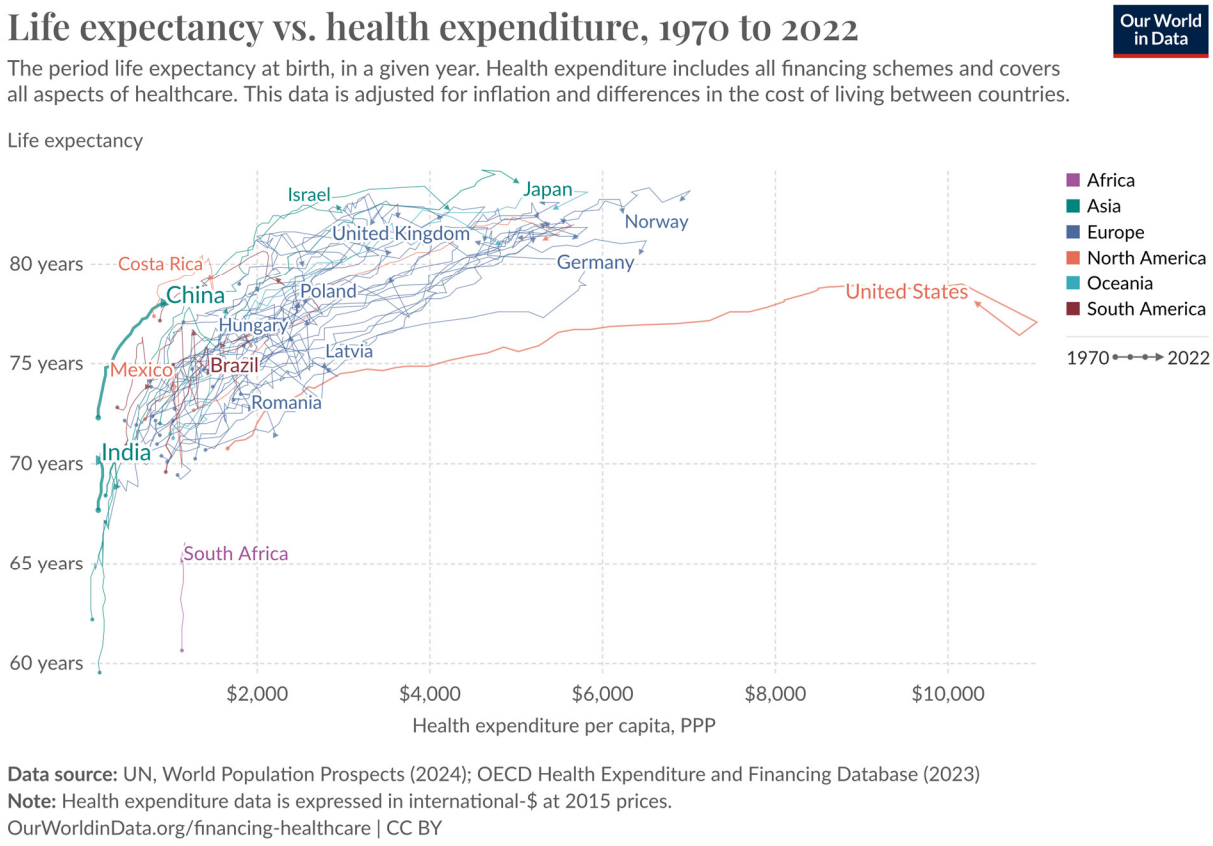
The idea for the Top 20 POEMs came from Roland Grad and Mark Ebell who publish these each year in the *American Family Physician*. The following are the POETs who generated the POEMs that served as the basis for the Top 20:

- Henry Barry
- Mark Ebell
- Nita Kulkarni
- Allen Shaughnessy
- Dave Slawson
- Linda Speer

This year's Top 20 POEMs was published online June 16, 2025.

Choosing Wisely

Much of the care provided in the US is expensive and doesn't really improve health as much as people are deluded about.



In response to the wastefulness in the US healthcare system, a family physician, Howard Brody, MD, PhD, wrote a commentary (N Engl J Med. 2010;362(4):283-5. www.ncbi.nlm.nih.gov/pubmed/20032315) challenging medical societies to identify the top 5 diagnostic tests or treatments within their specialties that are expensive and ineffective. This became

the basis for the Choosing Wisely campaign which launched in 2012. Sadly, Howard died July 2024 (humanmedicine.msu.edu/news/2024_In_Memoriam_Howard_Brody.html) but left behind this legacy. Many of the Top 20 POEMs of 2024 align with Choosing Wisely!

To select the Top 20 POEMs of 2024, each of the POETs selected up to 10 of their favorite POEMs published in 2024. The POETs, along with family medicine journal editors, scholars and practicing clinicians ranked each nominate POEM that summarized original research (i.e., they excluded guidelines) on the basis of:

- Relevance
- Potential to change practice
- Validity

This year, the Top 20 POEMs came in several groupings:

- Infectious diseases (6)
- Mental health and addiction (4)
- Cardiovascular disease (3)
- Diabetes (3)
- Gastroenterology (2)
- Miscellaneous (2)

Infectious Diseases

1. Probiotics reduce the likelihood of recurrence in women with frequent UTIs

Clinical question: Do oral or vaginal probiotics (or both) reduce the likelihood of recurrence in premenopausal adult women with frequent urinary tract infections?
Study design: Randomized controlled trial (double-blinded)
Funding source: Government
Allocation: Concealed
Setting: Outpatient (any)
Synopsis: This study from India identified 174 women aged 18 to 45 years who had experienced at least 3 uncomplicated urinary tract infections (UTIs) in the past year. The women's mean age was 36 years, and the mean number of UTIs in the previous year was slightly more than 5. The women were randomized into 1 of 4 groups: oral and vaginal placebos, oral probiotic and vaginal placebo, oral placebo and vaginal probiotic, or both oral and vaginal probiotics. The oral probiotic was 112.5 billion live lyophilized lactic acid bacteria and bifidobacteria; the vaginal probiotic contained 1 billion units of 3 lactobacilli strains. The groups were balanced at the start of the study, and analysis appears to have been by intention to treat. At 4 months, a symptomatic UTI had occurred in 70% in the placebo-only group, 61% in the oral probiotic group, 41% in the vaginal probiotic group, and 32% in the group that received both. The differences between placebo only and the active treatments were statistically significant for the vaginal and vaginal plus oral probiotic groups. Results at 12 months were similar, with rates of UTI of 95%, 77%, 61%, and 55%, respectively. Patients were asked to rate their degree of improvement and most in the vaginal and vaginal plus oral probiotic groups rated themselves as "much improved." No adverse events were reported (maybe they didn't look very hard, since placebo groups in every trial report adverse events).
Bottom line: Lactobacillus-containing probiotics (orally, vaginally, or both) reduce the incidence of recurrent UTI and prolong the time to the next UTI in premenopausal women with frequent UTIs. Vaginal probiotics (with or without oral probiotics) outperform oral probiotics alone. Vaginal probiotics alone provide a similar benefit to oral plus vaginal supplementation and would seem to be the least invasive and least costly option. (LOE = 1b)
Gupta V, Mastromarino P, Garg R. Effectiveness of prophylactic oral and/or vaginal probiotic supplementation in the preventing recurrent UTIs: A randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2024;78(5):1154-1161.

2. Community-acquired pneumonia: Most oral treatments are similarly effective

Clinical question: What is the best oral treatment for mild-to-moderate community-acquired pneumonia?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Self-funded or unfunded
Setting: Various (meta-analysis)
Synopsis: These researchers identified 24 randomized controlled trials of oral treatment in adults with image-confirmed mild-moderate community-acquired pneumonia by searching 2 databases, including Cochrane CENTRAL, as well as the reference lists of practice guidelines and review articles. They included all research written in 1 of 4 languages. Pairs of investigators selected articles for inclusion, abstracted the data, and evaluated the research for risk of bias. Since few studies compared antibiotics directly, the authors used a network meta-analysis to estimate differences in response. No antibiotic produced statistically superior results to clarithromycin. In comparison with clarithromycin, clinical response was best (but still similar to clarithromycin) with nemonoxacin, levofloxacin, and telithromycin. Nemonoxacin, levofloxacin, azithromycin, and amoxicillin/clavulanate led the pack for lower mortality. Penicillin and amoxicillin produced lower clinical response. Half the studies were deemed to be at high risk of bias due to breaches in modern conduct

of clinical trials (eg, not masking the participants and evaluators, selected reporting of outcomes, and so forth). There was no evidence of publication bias, but studies of doxycycline, a stalwart treatment of community-acquired pneumonia, were excluded since they were published so long ago.
Bottom line: Continue treating community-acquired pneumonia the way you're doing it. It's difficult, given the existing research data, to determine big differences in the clinical impact of the various oral antibiotics used for initial treatment. Using clarithromycin as the standard, telithromycin, azithromycin, amoxicillin/clavulanate, and the quinolones levofloxacin and nemonoxacin (available only in a few countries) produce similar benefits with regard to clinical response and mortality. Amoxicillin and penicillin may not work as well. Doxycycline, recommended in some guidelines, was not included in this analysis. (LOE = 1a)
Kurotschka PK, Bentivegna M, Hulme C, Ebell MH. Identifying the best initial oral antibiotics for adults with community-acquired pneumonia: A network meta-analysis. J Gen Intern Med 2024;39(7):1214-1226.

3. Single IM dose of nirsevimab reduces likelihood of hospitalization due to RSV in average-risk infants during first year of life (HARMONIE)

Clinical question: Does a single intramuscular injection of nirsevimab reduce the likelihood of hospitalization due to respiratory syncytial virus in newborns who do not meet criteria for receiving palivizumab?
Study design: Randomized controlled trial (nonblinded)
Funding source: Industry
Allocation: Concealed
Setting: Outpatient (any)
Synopsis: Nirsevimab is a monoclonal antibody against respiratory syncytial virus (RSV) that has recently been approved in the United States, Canada, and Europe. This study at 235 sites in France, Germany, and the United Kingdom identified 8058 infants born at 29 weeks' or later gestation who were not eligible for palivizumab, which is currently recommended for children at high risk of RSV complications and requires a monthly injection. The patients were recruited during their first winter and randomized to receive nirsevimab (50 mg if they weighed less than 5 kg and 100 mg if they weighed 5 kg or more) or usual care, in open-label fashion. The authors state that the vast majority of time the admitting physician was not an investigator, although they may well have been told of the medication by the parents. The primary outcome was hospitalization for lower respiratory infection with a positive test result for RSV, which occurred in 11 infants in the nirsevimab group and 60 in the usual care group (0.3% vs 1.5%; P < .001; number needed to treat [NNT] = 83). Severe RSV infection also occurred less often in the nirsevimab group (0.12% vs 0.47%; P = .004; NNT = 286). All subgroups by age, weight, sex, gestational age, and timing of randomization had similar benefits. Serious adverse events were rare and were similar between groups. According to the American Academy of Pediatrics, the cost of nirsevimab is approximately $495 for the one dose.
Bottom line: In average-risk infants, a single intramuscular dose of nirsevimab reduces the likelihood of hospitalization due to RSV. Although it's not inexpensive, nirsevimab is much less expensive than palivizumab and requires only a single dose. (LOE = 1b)
Drysdale SB, Cathie K, Flamein F, et al, for the HARMONIE Study Group. Nirsevimab for prevention of hospitalizations due to RSV in infants. N Engl J Med 2023;389(26):2425-2435.

4. Oral antivirals reduce hospitalization and death in immunocompromised vaccinated patients with COVID-19

Clinical question: Do oral antivirals reduce the likelihood of hospitalization or death for immunocompromised patients with mild to moderate symptomatic COVID-19?
Study design: Cohort (retrospective)
Funding source: Government
Setting: Outpatient (any)
Synopsis: To date, there have been no randomized trials of oral antivirals for COVID-19 in immunocompromised patients, so this propensity score–matched analysis provides the best evidence to date. In this Veterans Affairs study, the authors identified 390 immunocompromised patients (based on medication use [89%] or a comorbidity [11%]) who were diagnosed with COVID-19 and received an oral antiviral (molnupiravir or nirmatrelvir-ritonavir). Patients were recruited in early 2022 during the Omicron phase — 75% had received the full initial series of COVID-19 vaccinations and approximately 50% had received a booster. These patients were matched with 390 immunocompromised patients who were also diagnosed with COVID-19 during the study period but did not receive molnupiravir or nirmatrelvir-ritonavir. At 30 days, the composite of hospitalization or death was significantly lower in the treatment groups (5.9% for nirmatrelvir-ritonavir vs 5.8% for molnupiravir vs 14.6% for no treatment; P = .003; number needed to treat = 12). Reductions in the individual outcomes of hospitalization (5.5% to 5.8% vs 11.0%; P = .02) and mortality (0.0% to 0.4% vs 4.9%; P = .0002) were similar for the 2 drugs. The benefit was driven primarily by a reduction in deaths (0.3% vs 4.9%) and was greater with increasing degrees of vaccination.
Bottom line: In a mostly vaccinated, immunocompromised population, oral antivirals are associated with lower rates of hospitalization and mortality. This is different from the results of recent studies in immunocompetent populations in a similar time frame and with the Omicron variant. The baseline rates of hospitalization were much higher in this immunocompromised population than in studies of healthy adults, so it makes sense that the absolute benefit of the oral antivirals was also higher. (LOE = 2b)
Gentry CA, Nguyen PN, Thind SK, Kurdgelashvili G, Williams RJ 2nd. Characteristics and outcomes of US veterans with immunocompromised conditions at high risk of SARS-CoV-2 infection with or without receipt of oral antiviral agents. Clin Infect Dis 2024;78(2):330-337.

5. Benzyl benzoate 25% is much better than permethrin 5% for the treatment of scabies

Study design: Randomized controlled trial (double-blinded)

Funding source: Self-funded or unfunded
Allocation: Uncertain
Setting: Outpatient (any)
Synopsis: Researchers at one institution in Austria recruited 110 patients, 12 years and older, with dermoscopically diagnosed scabies. Patients with crusted scabies and those who had been treated in the previous 3 weeks were excluded. The patients' mean age was 28 years, 22% had been treated with topical permethrin, and 12% had been treated with oral ivermectin in the previous 3 months (the dosage of the latter, however, was often judged to have been inadequate). The patients were randomized to receive topical benzyl benzoate 25% or permethrin 5% daily for 3 days in a double-blind fashion. The primary outcome — absence of mites at 3 to 4 weeks after treatment — occurred significantly more often in the benzyl benzoate group (87% vs 27%; P < .001; number needed to treat [NNT] = 2). However, mild to moderate burning or stinging was reported more often by the benzyl benzoate group (43% vs 6%; P < .001; number needed to treat to harm = 3). The skin adverse events were short-lived and resolved spontaneously. Benzyl benzoate is widely available over the counter and is inexpensive.
Clinical question: Is benzyl benzoate 25% or permethrin 5% more effective for treating scabies in adolescents and adults?
Bottom line: Benzyl benzoate 25% was significantly more effective than permethrin 5% (NNT = 2). It was also associated with more skin irritation, but this adverse event was generally mild to moderate and transient. (LOE = 1b)
Meyersburg D, Hoellwerth M, Brandlmaier M, et al. Comparison of topical permethrin 5% vs. benzyl benzoate 25% treatment in scabies: a double-blinded randomized controlled trial. Br J Dermatol 2024;190(4):486-491.

6. Antibiotic treatment is effective for acute sinusitis in children

Clinical question: Is antibiotic treatment more effective than placebo in resolving symptoms of acute sinusitis in children?
Study design: Randomized controlled trial (double-blinded)
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: The authors searched 2 databases (though, curiously, not Cochrane CENTRAL) and identified 6 studies that compared an antibiotic, usually amoxicillin or amoxicillin/clavulanic acid (co-amoxiclav), with placebo in children at least one year of age with at least 10 days of symptoms of acute sinusitis. All but one study was conducted after the Haemophilus influenzae type b (Hib) vaccine was in widespread use. Treatment failure, defined in most studies as either worsening while using the treatment or a lack of improvement after 2 or so weeks of treatment, was significantly less common in patients who received an antibiotic, with 77% responding to treatment, than in patients who received a placebo (59% responding to treatment; number needed to treat = 6). Diarrhea was about twice as common with treatment. The number of the studies is too small to differentiate between different antibiotics or low-dose versus high-dose treatment. A single study was much larger than the rest combined and contributed most to the outcome. There was significant heterogeneity among the studies, which was removed when a low-quality study was removed from the analysis.
Bottom line: Though this study was a meta-analysis, the data largely come from a single study, which showed a substantial benefit, after a few weeks, to using amoxicillin with or without clavulanate to treat children with symptoms of acute sinusitis. (LOE = 1a)
Conway SJ, Mueller GD, Shaikh N. Antibiotics for acute sinusitis in children: A meta-analysis. Pediatrics 2024;153(5):e2023064244.

Mental health and addiction

7. Optimal smoking cessation treatments after initial treatment failure (#1)

Clinical question: What is the best subsequent strategy to attain smoking cessation in adults following initial treatment failure with varenicline or combined nicotine replacement therapy?
Study design: Randomized controlled trial (double-blinded)
Funding source: Foundation
Allocation: Concealed
Setting: Outpatient (primary care)
Synopsis: These investigators identified 490 adult smokers, aged 18 to 75 years, who smoked 5 or more cigarettes per day. The study participants randomly received (concealed allocation) assignment in phase 1 to receive either the standard dosage titration of varenicline or combined nicotine replacement therapy (CRNT; 21-mg patch plus at least six 2-mg lozenges per day) for weeks 1 to 6. In phase 2 (weeks 7 to 12), patients who met abstainer criteria (n = 142) continued their assigned medication. Nonabstainers (n = 348) were randomly assigned to (1) continue their phase 1 medication dosage, (2) increase their phase 1 medication dosage, or (3) switch to the alternate phase 1 medication for another 6 weeks. The increased varenicline dosage consisted of taking an extra 1-mg tablet (3 mg total daily dosage) with the evening dose, and the increased CNRT dose consisted of an additional 21-mg nicotine patch (42 mg total daily) plus continuing lozenges. Masking of patients, physicians, and study personnel occurred via inactive matched placebos using the same dosing regimen. Smoking abstinence was confirmed by self-report of no smoking in previous 7 days plus expired carbon monoxide of less than 6 ppm at week 12.
The analysis was by intention to treat. Of the nonabstainers who were initially treated with standard-dose varenicline, confirmed abstinence occurred significantly more among often patients who increased their varenicline dosage compared with either switching to CNRT or continuing their initial varenicline dose (20% vs 0% and 3%, respectively). Of the nonabstainers who were initially treated with CNRT, confirmed abstinence occurred significantly more often among patients who either switched to varenicline or increased the CNRT dosage compared with continuing the initial CNRT dosage (14% and 14% vs 8%, respectively).
Bottom line: For patients who failed to attain smoking abstinence at 6 weeks after initial treatment with varenicline, increasing the dosing of varenicline (from 2 mg to 3 mg daily) resulted in a significantly higher quit rate than continuing to use the same dosage for a longer period. Switching to CNRT was not effective for attaining smoking abstinence. For similar patients who failed on initial treatment with CNRT, an increased dosage of CNRT (from 21-mg patch to 42-mg patch plus lozenges) or switching to varenicline resulted in a significantly higher quit rate than continuing to use the same dosage of CNRT. (LOE = 1b)

Cinciripini PM, Green CE, Shete S, et al. Smoking cessation after initial treatment failure with varenicline or nicotine replacement. A randomized clinical trial. JAMA 2024;331(20):1722-1731.

8. Acamprosate and oral naltrexone are useful for treating alcohol use disorder

Clinical question: What medications are safe and effective for the treatment of alcohol use disorder?
Study design: Systematic review
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: These investigators searched multiple databases — including PubMed, the Cochrane Library, PsycINFO, and EMBASE — for English-language studies of adults, 18 years or older, that evaluated the efficacy of pharmacotherapy for alcohol use disorder. Eligible studies included randomized trials that compared active therapy for at least 12 weeks with placebo or another medication in an outpatient setting. Two investigators independently assessed articles for inclusion and risk of bias using a standardized scoring tool. Disagreements were resolved by consensus discussion with a third reviewer. A total of 156 articles described the results of 118 randomized controlled trials of various pharmacotherapies. Of these, 37 were new since a previous systematic review was published in 2014.
Overall, the strength of evidence best supported acamprosate and oral naltrexone (50 mg/day) for reducing the risk of returning to any drinking (number needed to treat [NNT] = 11 and 18, respectively). Oral naltrexone was also associated with a significantly reduced risk of return to heavy drinking (NNT = 11). Injectable naltrexone was not associated with lower rates of return to any drinking or heavy drinking but was significantly more effective than placebo in reducing the percentage of drinking days and heavy drinking days. Acamprosate was not significantly better than placebo for reducing the risk of return to heavy drinking. Summary evidence did not support a benefit of disulfiram or gabapentin compared with placebo. Compared with placebo, topiramate was only significantly associated with a reduction in the mean percentage of drinking days and number of drinks per day. Similarly, the data for the effectiveness of baclofen were graded as having low strength of evidence. The most commonly reported adverse events for acamprosate were gastrointestinal problems (e.g., nausea, diarrhea); for naltrexone, the most commonly reported adverse events were anxiety and dizziness. None of the trials reported evidence that any pharmacotherapies significantly affected other patient-oriented outcomes, such as quality of life, motor vehicle accidents and injuries, and mortality. The authors provided no formal evaluation of publication bias or heterogeneity/homogeneity of results.
Bottom line: This updated systematic review found that, in conjunction with psychosocial interventions, oral naltrexone (50 mg/day) and oral acamprosate have the strongest evidence for the effective treatment of alcohol use disorder. (LOE = 1a)
McPheeters M, O'Connor EA, Riley S, et al. Pharmacotherapy for alcohol use disorder. A systematic review and meta-analysis. JAMA 2023;330(17):1653-1665.

9. CBT is effective for patients with fatigue associated with long COVID

Clinical question: Does cognitive behavioral therapy improve fatigue in patients with long COVID?
Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Concealed
Setting: Outpatient (any)
Synopsis: Severe fatigue is a prominent and potentially disabling component of post-acute COVID-19 syndrome, or "long COVID." This trial identified 114 Dutch adults with severe fatigue beginning with COVID-19, or substantially worsened by it, and persisting for 3 months to 12 months following the onset of the acute infection. They were randomized to a mean of 18 weeks of cognitive behavioral therapy (CBT) or care as usual. The groups were balanced at baseline with a mean age of 46 years, 11% had been hospitalized for COVID-19, 99% were unvaccinated, and 73% were female. Analysis was by intention to treat, with only 3 or 4 patients lost to follow-up in each group. The CBT intervention included goal setting, targeting a regular sleep-wake pattern, developing helpful thinking patterns, developing social support, implementing graded increases in activity, and several other components. It was delivered via online modules or telemedicine because of the pandemic. (More details about the intervention can be found in a supplementary appendix to the study.) The primary outcome was the score on the 20-item Checklist Individual Strength (CIS; range 8 - 56), with higher scores indicating worse fatigue. At baseline, this score was 48 points in both groups. Clinical response was evaluated at 19 weeks (end of treatment) and at 26 weeks. The difference in fatigue scores at 19 weeks (-9.3 points; 95% CI -13.2 to -5.3) and 26 weeks (-8.4 points, 95% CI -13.1 to -3.7) both favored CBT and would be considered clinically significant. The percentage of patients no longer having severe fatigue (CIS score < 35 points) was much higher for the CBT group at 26 weeks (63% vs 26%; P < .001; number needed to treat = 3). Other secondary outcomes also favored CBT, and no serious adverse events occurred.
Bottom line: For patients with severe fatigue at least 3 months after COVID-19, CBT offers significant improvement in symptoms over care as usual. (LOE = 1b)
Kuut TA, Müller F, Csorba I, et al. Efficacy of cognitive-behavioral therapy targeting severe fatigue following coronavirus disease 2019: Results of a randomized controlled trial. Clin Infect Dis 2023;77(5):687-695.

10. Electronic nicotine-delivery systems increase abstinence in tobacco users

Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Concealed
Setting: Population-based
Synopsis: Swiss adults who smoked at least 5 cigarettes per day and were interested in quitting were randomized into 2 groups. The control group received smoking cessation counseling, including cognitive behavioral therapy, motivational interviewing, and shared decision-making for the use of drugs that support smoking cessation, including nicotine replacement therapy and smoking cessation

medications. They also received $50 vouchers that could be used for any purpose. The intervention group received all of that plus 2 e-cigarette starter kits, replacement coils, and e-liquids containing from 0 to 19.6 mg of nicotine (participants could choose the dose of nicotine they preferred). At baseline, the groups were similar: a median age of 38 years, 47% were female, the median age that they started smoking was 16 years, and they smoked a median of 15 cigarettes per day. Allocation to groups was concealed but otherwise it was an open-label trial. A total of 1246 participants were randomized, and analysis was by intention to treat. The primary outcome was biochemically verified continuous abstinence from tobacco from the target quit date to 6 months. This occurred significantly more often in the intervention group (28.9% vs 16.3%; absolute difference 12.6%; 95% CI 8% - 17.2%; number needed to treat [NNT] = 8). However, abstinence from any nicotine use was higher in the control group (33.7% vs 20.1%; NNT = 8). Not all patients underwent biochemical verification — if you believe the patients, the quit rates were even higher (38.1% vs 23.4%; NNT = 7). Abstinence that was not continuous but had been present for the last 7 days with biochemical verification was also greater with the intervention (39.4% vs 21.3%; NNT = 6). More patients in the intervention group reported absence of cough (41% vs 34%) and phlegm (62% vs 51%), though the differing response rates between the 2 groups could have biased these results. Serious adverse events were uncommon and similar between groups.
Clinical question: For smokers who want to quit, do electronic nicotine-delivery systems increase the likelihood of abstinence at 6 months?
Bottom line: Adult smokers who are given e-cigarettes are significantly more likely to be abstinent at 6 months (NNT = 6 - 8). In this study, the cost of e-cigarettes was paid by the study, so in the real world where patients have to buy their own e-cigarettes the results may be less favorable. (LOE = 1b-)
Auer R, Schoeni A, Humair JP, et al. Electronic nicotine-delivery systems for smoking cessation. N Engl J Med 2024;390(7):601-610.

Cardiovascular disease

11. Semaglutide reduces mortality and cardiovascular (CV) events in obese patients with CV disease but no diabetes

Clinical question: In obese patients with established cardiovascular disease (but not diabetes), does semaglutide improve cardiovascular outcomes?
Study design: Randomized controlled trial (double-blinded)
Funding source: Industry
Setting: Outpatient (any)
Synopsis: These researchers identified adults who were 45 years and older with a body mass index of at least 27 kg/m^2, had established cardiovascular disease, and who did not have diabetes mellitus. The 17,604 patients were randomized to receive a once-weekly semaglutide subcutaneous injection, beginning at 0.24 mg and escalating to a maximum tolerated dose of up 2.4 mg over 16 weeks, or to placebo. At baseline, the groups were nearly identical, with a mean age of 62 years, 72% were men, 84% were white, and they had a mean body mass index of 33 kg/m^2. Approximately two-thirds of patients had a previous myocardial infarction (MI), 18% had a stroke, 4% had peripheral arterial disease, and 8% had 2 or more of these previous events. Patients were treated for a mean of 34 months and were followed up for a mean of 40 months, with more patients in the semaglutide group discontinuing the study drug (16% vs 8%). The primary composite of cardiovascular death, nonfatal MI, or nonfatal stroke occurred less often in the treatment group (6.5% vs 8.0%; P < .001; number needed to treat [NNT] = 67 over 40 months). With regard to individual endpoints, nonfatal MI was the only endpoint that decreased significantly (2.7% vs 3.7%; P < .05; NNT = 100 over 40 months). Although cardiovascular mortality was not significantly decreased (2.5% vs 3.0%; P = .07), all-cause mortality was (4.3% vs 5.2%; P < .05; NNT = 111 over 40 months). Since the authors didn't adjust for multiple comparisons and all-cause mortality was a secondary outcome, the statistical significance should be taken with a grain of salt. Patients in the semaglutide group also lost approximately 9% of their body weight, compared with essentially no change in the placebo group.
Bottom line: For obese patients with established cardiovascular disease who do not have diabetes, semaglutide decreases the risk of nonfatal MI (NNT = 100) but not cardiovascular mortality (2.5% vs 3.0%, P = .07) over 40 months of follow-up. It is interesting that the title of this industry-sponsored study says nothing of the fact that this was a group of patients with established heart disease. Perhaps they hope that we will fall prey to indication creep and give it to anyone who is obese? (LOE = 1b)
Lincoff AM, Brown-Frandsen K, Colhoun HM, et al, for the SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 2023; 389(24):2221-2232.

12. SGLT2 inhibitors = little effect on glycemic control or all-cause mortality, but decrease CV deaths in older adults with T2DM plus heart failure

Clinical question: Do sodium-glucose cotransporter-2 inhibitors improve outcomes in frail adults or elderly adults with type 2 diabetes mellitus and heart failure?
Study design: Meta-analysis (other)
Funding source: Self-funded or unfunded
Setting: Various (meta-analysis)
Synopsis: These authors searched multiple databases and registries to identify randomized trials and observational studies that compared sodium-glucose cotransporter-2 (SGLT2) inhibitors with either a placebo or another glucose-lowering agent in adults who are frail or 65 years or older. The participants had to have type 2 diabetes mellitus (T2DM) plus heart failure, and the studies had to be published in English. The authors used validated tools to assess the methodologic quality of the included studies. Overall, they identified 22 reports from 20 studies (77,083 participants, of which 57% were male). Ten of the studies were randomized trials, 7 were observational studies, and 3 were secondary analyses. Seventeen of the studies (19 reports) provided data suitable for pooling. The authors of this meta-analysis report the randomized trials were generally at low risk of bias, but half the studies lacked adequate masking of participants and study personnel, half the studies lacked clarity about the masking of outcomes, and several had other

areas of uncertainty. Overall, there was no significant difference in glycemic control, however, the data were significantly heterogeneous (I^2 = 66%). One trial found the SGLT2 inhibitors resulted in significantly worse glycemic control; removing this study resolved the heterogeneity (I^2 = 0%) and the net effect was that the SGLT2 inhibitors were associated with a small but statistically significant improvement in glycemic control (0.24% reduction in glycohemoglobin). The SGLT2 inhibitors were also associated with fewer deaths from any cause (relative risk [RR] = 0.84; 95% CI 0.69 - 0.95), though there was no significant difference in the randomized trials. However, the SGLT2 inhibitors were associated with fewer cardiac deaths (RR = 0.80; 0.69 - 0.94) and these findings were consistent independent of study design. The SGLT2 inhibitors were also associated with fewer hospitalizations for heart failure (RR = 0.69; 0.59 - 0.81) and these data were consistent across study designs. Finally, the SGLT2 inhibitors were not associated with reducing other outcomes, such as acute coronary events, cerebrovascular events, worsening renal function, heart failure, or diabetic ketoacidosis.
Bottom line: Overall, in this analysis that pooled data from disparate study designs, SGLT2 inhibitors have little effect on glycemic control or all-cause mortality but decrease CV deaths in elderly or frail adults with T2DM plus heart failure. (LOE = 2a-)
Aldafas R, Crabtree T, Alkharaiji M, Vinogradova Y, Idris I. Sodium-glucose cotransporter-2 inhibitors (SGLT2) in frail or older people with type 2 diabetes and heart failure: a systematic review and meta-analysis. Age Ageing 2024;53(1):afad254.

13. For patients with AMI and preserved ejection fraction, long-term beta-blockers do not improve outcomes (REDUCE-AMI)

Clinical question: In patients with preserved ejection fraction following an acute myocardial infarction (AMI), does long-term use of a beta-blocker reduce the likelihood of death or new AMI?
Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Concealed
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: This trial recruited adults within 7 days of AMI who had an ejection fraction of at least 50% based on angiography or echocardiography and at least one ≥ 50% obstructed coronary artery. At baseline, these 5020 patients, predominantly from Sweden and New Zealand, had a median age of 65 years, 22% were female, and 55.4% had single vessel disease. At the time of discharge, 97% were taking aspirin, 80% were taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and 99% were using a statin. Groups were balanced at baseline and analysis was by intention to treat. The patients were randomized to receive a beta-blocker (62.2% received metoprolol, 37.8% received bisoprolol) or no beta-blocker. Ultimately, only 9.8% in the no beta-blocker group took one. Patients were followed up for a median of 3.5 years. There was no difference in the likelihood of death or AMI between groups (7.9% beta-blocker vs 8.3% no beta-blocker; P = .64). There was also no difference in secondary endpoints, including all-cause mortality, cardiovascular mortality, AMI, and hospitalization for atrial fibrillation or heart failure. The number of hospitalizations for potential adverse effects of beta-blockers was not increased.
Bottom line: For patients with AMI and preserved ejection fraction, the use of a beta-blocker for 3.5 years did not reduce the likelihood of death or a new AMI. (LOE = 1b-)
Yndigegn T, Lindahl B, Mars K, et al, for the REDUCE-AMI Investigators. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med 2024;390(15):1372-1381.

Diabetes

14. Continuous or intermittent glucose monitoring not effective, perhaps harmful

Clinical question: Does continuous glucose monitoring offer a benefit over traditional glucose self-monitoring in patients with type 2 diabetes?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: The researchers searched 4 databases, including Cochrane CENTRAL, and reference lists of retrieved articles to find randomized studies in any language of continuous glucose monitoring (CGM) and intermittently scanned continuous glucose monitoring (isCGM) devices, identifying 26 studies of 2783 patients. Following PRISMA guidelines, 2 authors selected articles for inclusion and one author abstracted the data, which were checked by another author. Most studies were relatively short term (8 to 12 weeks in duration). CGM had a small effect on reducing HbA1c levels (0.19% [percent, not percentage points] lower) but had no effect, over the short term, on body composition, blood pressure, or lipid levels. However, in the 3 studies that evaluated it, user satisfaction was lower with the use of the device and adverse effects were higher (relative risk [RR] 1.22; 95% CI 1.01 - 1.47). isCGM devices, on average, decreased HbA1c by 0.31% but also had no effect on body composition, blood pressure, or lipid levels. User satisfaction was improved with these devices, but adverse events were also more likely (RR 1.30; 1.05 - 1.62).
Bottom line: In relatively short-term studies, glucose monitoring devices have only a small effect on HbA1c and do not affect body composition, lipids, or blood pressure. Real-time (continuous) glucose monitors, such as Dexcom G6 and G5, Medtrum Touch Care Nano, and Medtronic Guardian models, may cause psychological stress in users. Intermittent glucose monitors, such as FreeStyle Libre, are better accepted by patients. Note: Both types of devices *increase* the risk of adverse effects. (LOE = 1a)
Seidu S, Kunutsor SK, Ajjan RA, Choudhary P. Efficacy and safety of continuous glucose monitoring and intermittently scanned continuous glucose monitoring in patients with type 2 diabetes: a systematic review and meta-analysis of interventional evidence. Diabetes Care 2024;47(1):169-179.

15. SGLT2 inhibitors, GLP1 agonists provide greater benefit for patients with T2D

Clinical question: Which of the new treatments for patients with type 2 diabetes affect mortality, cardiovascular outcomes, and renal outcomes?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Self-funded or unfunded
Setting: Various (meta-analysis)
Synopsis: These researchers searched 4 databases and identified 84 randomized studies of the effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP1) agonists, dipeptidyl peptidase-4 (DPP4) inhibitors, and long-acting insulins as monotherapy or combination therapy in adults with type 2 diabetes mellitus (T2DM). These are large studies of middle-aged adults with long-standing (mean 8.8 years) T2DM and co-morbidities, such as hypertension or tobacco use, who were evaluated for a mean of almost 2 years. Data were abstracted by one investigator and verified by a second, and 2 reviewers independently assessed the risk of bias. The authors used direct and indirect comparisons of the treatments via network meta-analysis. Based on high certainty of evidence, SGLT2 inhibitors and GLP1 agonists reduce all-cause mortality and major adverse cardiovascular events compared with usual care. SGLT2 inhibitors reduce the progression of chronic kidney disease and heart failure hospitalizations and GLP1 agonists reduce stroke. Both SGLT2 inhibitors and GLP1 agonists outperform insulin with regard to all-cause mortality. Long-acting insulins and DPP4 inhibitors are no more effective than usual care to prevent harms. The risk of severe hypoglycemia is lower with SGLT2 inhibitors and GLP1 agonists.
Bottom line: Of the new treatments for people with type 2 diabetes, SGLT2 inhibitors and GLP1 agonists outperform DPP4 inhibitors and long-acting insulins as monotherapy or combination therapy in adults with T2DM, reducing all-cause mortality, major cardiovascular events, chronic kidney disease, and heart failure. SGLT2 inhibitors and GLP1 agonists are also less likely to cause severe hypoglycemia. (LOE = 1a)
Drake T, Landsteiner A, Langsetmo L, et al. Newer pharmacologic treatments in adults with type 2 diabetes: a systematic review and network meta-analysis for the American College of Physicians. Ann Intern Med 2024 May;177(5):618-632.

16. Among overweight or obese adults, phentermine-topiramate and GLP-1 receptor agonists are the most effective for promoting weight loss

Clinical question: Which drugs are the most effective for achieving weight loss in overweight or obese adults?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Foundation
Setting: Various (meta-analysis)
Synopsis: These authors searched databases, registries, and reference lists to identify randomized trials of drugs to promote weight loss in overweight or obese adults, regardless of comorbidities. The trials had to be at least 12 weeks long, published in English, and could not systematically recruit adults with psychological conditions. The authors chose 5% weight reduction as the minimal important difference, which is consistent with other studies and recommendations. They included 132 unique trials with 48,209 adults. The participants were generally young (median 47 years of age), 76% were female, and the average body mass index was 35.3 kg/m². The median study duration was 24 weeks. The authors reported the included studies had issues related to study deviations, missing outcome data, and missing adverse event data. To determine the comparative effectiveness of the different drugs, the authors performed a network meta-analysis. All the drugs (combined with lifestyle modifications) were more effective than lifestyle interventions alone at achieving weight loss. The combination of phentermine-topiramate was the most effective at inducing at least a 5% weight loss (odds ratio [OR] 8.02; 95% CI 5.24 - 12.27; mean weight loss 7.98%), followed by the GLP-1 receptor agonists (OR 6.33; 5.00 - 8·00; mean weight loss 5.79%). Naltrexone-bupropion, phentermine-topiramate, GLP-1 receptor agonists, and orlistat had the greatest likelihoods of discontinuation due to adverse effects (ORs 2.69, 2.40, 2.22, and 1.71, respectively). After conducting additional post hoc analyses, the authors conclude that semaglutide, a GLP-1 receptor agonist, was the most effective at achieving at least a 5% weight loss (OR 9.82) and a similar rate of adverse events as other drugs. However, post hoc analyses are fraught with peril and probably best used to generate hypotheses. What happened with the SGLT2 inhibitors? In this analysis, they were in the middle of the pack: slightly more effective than lifestyle modification at achieving at least 5% weight loss (2.07% weight loss from baseline; OR 2.88) with a comparable likelihood of discontinuation due to adverse effects (OR 1.42). Unlike many network meta-analyses researchers, these authors provided additional data on the incremental effects of the various drugs (compared with lifestyle modification) on weight loss and drug discontinuations. The following table translates these data into numbers needed to treat (NNT) and numbers needed to treat to harm (NNTH). Note: These data simulate direct comparisons and are not based on actual head-to-head data.

Drug	NNT 5% or greater weight loss	NNT 10% or greater weight loss	NNTH discontinuation
Phentermine-topiramate	2	3	18
GLP-1 agonists	3	3	20
Naltrexone-bupropion	3	4	15
Orlistat	5	9	34
Metformin	6	NS	NS
SGLT2 inhibitors	5	NS	NS

Bottom line: Phentermine-topiramate and GLP-1 receptor agonists were the most effective drugs for achieving weight loss in overweight or obese adults. (LOE = 1a-)
Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. Lancet 2024;403(10434):e21-e31.

Gastroenterology

17. Amitriptyline as second-line therapy improves symptoms in adults with irritable bowel syndrome (ATLANTIS)

Clinical question: Does titrated low-dose amitriptyline improve symptoms in adults with irritable bowel syndrome who have failed first-line therapies?
Study design: Randomized controlled trial (double-blinded)
Funding source: Government
Allocation: Concealed
Setting: Outpatient (primary care)
Synopsis: These researchers recruited adults with irritable bowel syndrome (IBS) from primary care practices in the United Kingdom. To be included, the participants could have IBS of any subtype but had to have failed first-line treatments (diet, lifestyle, antispasmodics, laxatives, or antidiarrheals) and have at least moderate severity on the IBS Severity Scoring System (IBS-SSS). The researchers randomized the patients to receive titrated low-dose amitriptyline (n = 232) or matching placebo (n = 231). More than 80% of the participants had IBS with diarrhea (IBS-D) or with mixed diarrhea and constipation (IBS-M). The initial dose of amitriptyline was 10 mg every evening and the dose was increased over 3 weeks to a maximum of 30 mg. The researchers built in many overdose safeguards, such as assessing depression and suicidality and limiting the number of pills given to participants. Over the 6 months of the study, in addition to completing the IBS-SSS, the participants were asked "Have you had adequate relief of your IBS symptoms?" At the end of 6 months, a worrisome 23% discontinued their trial medication (20% of the amitriptyline-treated patients and 26% of placebo-treated patients) — the most common reason being adverse events. After 6 months, participants in both groups improved, but the amitriptyline-treated participants had a greater degree of improvement: 27 points better in their intention-to-treat analysis; the authors report, however, that 35 points is the minimum clinically important difference. More important, 61% of the amitriptyline-treated group reported meaningful improvement compared with 45% of those receiving placebo (number needed to treat = 7; 95% CI 4 - 16). These findings are consistent with guidelines from the American College of Gastroenterology and the British Society of Gastroenterology. The authors also provide a patient guide to self-titration of amitriptyline. Finally, this paper was recognized as a distinguished paper at the 2023 meeting of the North American Primary Care Research Group.
Bottom line: In this study, composed largely of adults with IBS-D and IBS-M with at least moderate severity despite first-line therapy, titrated low dose amitriptyline was more effective than placebo in improving symptoms. (LOE = 1b)
Ford AC, Wright-Hughes A, Alderson SL, et al, for ATLANTIS trialists. Amitriptyline at low-dose and titrated for irritable bowel syndrome as second-line treatment in primary care (ATLANTIS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023;402(10414):1773-85.

18. Wait-and-watch is an option for patients with symptomatic gallstones

Clinical question: Is it safe to watch patients with symptomatic gallstone disease without complications?
Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Concealed
Setting: Inpatient (ward only)
Synopsis: These British researchers enrolled 434 adults with uncomplicated symptomatic gallstone disease referred to secondary care. The patients received, using concealed allocation, either conservative management or laparoscopic cholecystectomy. Patients were excluded if they had evidence or history of common bile duct gallstones, acute pancreatitis, obstructive jaundice, or infection. A total of 67% of the participants assigned to surgery over the next 18 months and 25% of the participants assigned to conservative management ended up in surgery. The intention-to-treat analysis, in which patients were evaluated in their original group (despite crossover to the other group), showed that pain scores over the 18 months were similar in both groups. In addition, quality of life, measured by quality-adjusted life years, was similar in both groups. In the UK, the conservative approach saved £1033 ($1334; €1205) over time after accounting for health sources use over 18 months.
Bottom line: Patients with uncomplicated gallstones can be managed over time with analgesia and monitoring, but approximately 25% will eventually need cholecystectomy over the next 18 months. Still, there appears to be no need to rush to surgery without evidence of common bile duct blockage or acute pancreatitis. (LOE = 1b-)
Ahmed I, Hudson J, et al, for the C-GALL Study Group. Effectiveness of conservative management versus laparoscopic cholecystectomy in the prevention of recurrent symptoms and complications in adults with uncomplicated symptomatic gallstone disease (C-GALL trial): pragmatic, multicentre randomised controlled trial. BMJ 2023;383:e075383.

Miscellaneous

19. Monoclonal antibodies for Alzheimer disease: A lack of clinically meaningful benefits, plus significant harms

Clinical question: Does treatment with monoclonal antibody therapy that targets amyloid improve patient outcomes?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Unknown/not stated
Setting: Various (meta-analysis)
Synopsis: The authors of this systematic review and meta-analysis of randomized controlled trials sought to determine whether monoclonal antibody medications that target amyloid for the treatment of Alzheimer disease provide clinically meaningful patient-

oriented benefits or harms. This is an important question because federal approval of these medications was based on surrogate markers. The authors included 19 studies with 23,202 participants. Inclusion criteria included the enrollment of adults with cognitive impairment, Alzheimer disease of any severity, or a high risk of Alzheimer disease with at least one year duration, and the reporting of an outcome of interest. The authors excluded trials or trial arms that used doses lower than those approved by the US Food and Drug Administration. All studies were industry-funded placebo-controlled trials. Most studies enrolled patients with mild cognitive impairment or mild to moderate Alzheimer disease. Outcomes of interest were well-defined minimum clinically important differences (MCIDs) in the results for any of multiple cognitive scoring tools and potential harms. The drugs used in the trials included in this meta-analysis were solenezumab, aducanumab, and lecanemab, donanemab, and bapineuzumab. Notably, there are no head-to-head trials with other drugs. The summary analysis showed that improvement over placebo was small (standard mean difference [SMD] -0.07; 95% CI -0.10 to 0.04). Although some statistically significant benefits were identified, none were close to reaching an MCID threshold. There was no overall difference between treatment and control groups for all-cause mortality, though bapineuzumab was associated with an increase (relative risk [RR] 1.76; 1.03 - 3.00; number needed to treat to harm [NNTH] = 102). The most frequently reported harms were amyloid-related imaging abnormalities, including edema (ARIA-E) (RR in overall analysis 10.3; 7.4 - 14.3; NNTH = 9), symptomatic ARIA-E (RR for the 3 drugs reporting = 24.3; 9.9 - 59.9; NNTH = 86), and hemorrhage (ARIA-H; RR = 1.74; 1.2 - 2.4; NNTH = 13).
Bottom line: To date, amyloid-targeting antibodies for the treatment of Alzheimer disease have failed to demonstrate clinical meaningful benefits. They are associated with concerning risks of harm, most notably cerebral hemorrhage identified on imaging studies (NNTH = 13). The balance of risk versus benefit demonstrated thus far doesn't justify the use of these costly (> US$20,000 annually) drugs. (LOE = 1a)
Ebell MH, Barry HC, Baduni K, Grasso G. Clinically important benefits and harms of monoclonal antibodies targeting amyloid for the treatment of Alzheimer disease: A systematic review and meta-analysis. Ann Fam Med 2024;22(1):50-58.

20. Delivery of bad news via phone = in-person delivery

Clinical question: Does delivery of bad news via telephone increase psychological stress more than in-person communication?
Study design: Meta-analysis (other)
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: These researchers searched 4 databases and reference lists of screened articles to identify 11 observational and randomized controlled trials that investigated differences in psychological distress of breaking bad news by telephone compared with in person in patients or next of kin. Two authors independently selected articles for inclusion and abstracted the relevant data. Most (7) of the studies evaluated disclosure of malignancy diagnoses; the rest included results of genetic testing, Alzheimer disease, and hypertrophic cardiomyopathy. Overall, the study quality was moderate to good. There was no difference regarding psychological distress when bad news was delivered via telephone in terms of anxiety (3 studies, 285 participants), depression (3 studies, 284 participants), and post-traumatic stress disorder (2 studies, 171 participants). Results were similar for satisfaction with care. In a single study, there was no association between level of trust, which was high, and disclosure of bad news via telephone versus in person.
Bottom line: Delivering bad news by telephone does not affect levels of anxiety, depression, or satisfaction with care as compared with delivering the news in person. (LOE = 2a)
Mueller J, Beck K, Loretz N, et al. The disclosure of bad news over the phone vs. in person and its association with psychological distress: a systematic review and meta-analysis. J Gen Intern Med 2023;38(16):3589-3603.

Bonus POEM

The following POEM generated a bit of controversy among the voters. It was either given the highest possible rating or the lowest possible rating! The naysayers reported that the study had a small effect, represented an infrequent scenario, and it was unlikely that primary care clinicians would be making the decision!

21. Greater risk of serious bleeding with diltiazem vs metoprolol in adults with atrial fibrillation using apixaban or rivaroxaban

Clinical question: Are adults with atrial fibrillation who take apixaban or rivaroxaban at increased risk of serious bleeding from diltiazem or metoprolol for rate control?
Study design: Cohort (retrospective)
Funding source: Government
Setting: Population-based
Synopsis: The most commonly prescribed direct oral anticoagulants — apixaban and rivaroxaban — are metabolized and eliminated by hepatic cytochrome P450 enzymes. Diltiazem is commonly prescribed for adults with atrial fibrillation (AF) and is a strong inhibitor of cytochrome P450. Thus, concurrent use with apixaban or rivaroxaban may significantly increase the risk of serious bleeding events. These investigators analyzed data from multiple Medicare registries to identify adults with a diagnosis of AF, aged 65 years or older, who filled a prescription for apixaban or rivaroxaban (N = 204,155). Eligible study participants included those who were concurrently filling a prescription for diltiazem (n = 53,275) or metoprolol (n = 150,880). Multiple adjustments occurred to control for potential confounders, including frailty status, cardiovascular disease, chronic kidney disease, cancer, and other medication use that could potentially inhibit the P450 system. Summary measures of risk for stroke or hemorrhage were versions of the CHA_2DS_2-VASc score and the HAS-BLED score. During 90,927 person-years of follow-up, serious bleeding events resulting in hospitalization or death occurred significantly more often in patients taking diltiazem versus metoprolol (60.3 vs 49.7 events per 1000 person-years; relative difference of 10.6; 95% CI 7.0 -14.2). No significant differences occurred in the risk for ischemic or hemorrhagic stroke, systemic embolism, or death not related to bleeding. Risk was highest for patients treated with a diltiazem dose of 120 mg per day or higher (NNTH = 15 additional cases for every 1000 person years). Risk was also increased in patients with a HAS-BLED score of 4 or higher and in those taking rivaroxaban.

Bottom line: Adults with AF who take apixaban or rivaroxaban for stroke prevention are at a significantly increased risk of serious bleeding with the concurrent use of diltiazem compared with metoprolol for rate control. The risk is highest in patients taking diltiazem doses higher than 120 mg per day, with HAS-BLED scores of 4 or higher, and taking rivaroxaban compared with apixaban. (LOE = 2b)
Ray WA, Chung CP, Stein CM, et al. Serious bleeding in patients with atrial fibrillation using diltiazem with apixaban or rivaroxaban. JAMA 2024;331(18):1565-1575.

Rank Order of the Top 20 POEMs

Rank	Title of POEM
1	Optimal smoking cessation treatments after initial treatment failure
2	Continuous or intermittent glucose monitoring not effective, perhaps harmful
3	Probiotics reduce the likelihood of recurrence in women with frequent urinary tract infections
4	Acamprosate and oral naltrexone are useful for the treatment of alcohol use disorder
5	Community-acquired pneumonia: Most oral treatments are similarly effective
6	SGLT2 inhibitors, GLP1 agonists provide greater benefit for patients with type 2 diabetes
7	Lack of clinically meaningful benefits plus significant harms of monoclonal antibodies for Alzheimer's
8	Single IM dose of nirsevimab reduces likelihood of hospitalization due to RSV in average-risk infants during first year of life (HARMONIE)
9	Amitriptyline as second-line therapy improves symptoms in adults with irritable bowel syndrome (ATLANTIS)
10	Among overweight or obese adults, phentermine-topiramate and GLP-1 receptor agonists are the most effective for promoting weight loss
11	Cognitive behavioral therapy effective for patients with fatigue associated with long COVID
12	Semaglutide reduces mortality and cardiovascular (CV) events in obese patients with CV disease but no diabetes
13	Electronic nicotine-delivery systems increase abstinence in tobacco users (NNT = 6 - 8)
14	Oral antivirals reduce hospitalization and death in immunocompromised vaccinated patients with COVID-19
15	ACG guideline on treating adults infected with Helicobacter pylori
16	Benzyl benzoate is 25% much more effective than permethrin 5% for the treatment of scabies
17	Wait-and-watch is an option for patients with symptomatic but uncomplicated gallstones
18	Delivery of bad news via phone = in-person delivery
19	Antibiotic treatment is effective for acute sinusitis in children
20	SGLT2 inhibitors = little effect on glycemic control or all-cause mortality, but decrease CV deaths in older adults with T2DM plus heart failure

Bottom Lines:

- There is a lot of research out there, while a small proportion is relevant to the care provided by primary care clinicians, it adds up

- Pay attention to guideline developers using good development methods (e.g., ACP, AAFP, NICE)
- The American Family Physician publishes short critical research summaries to help you stay current
- Free podcast – Primary Care Update – 30 minutes every 2 weeks covering 3-4 recent POEMs with commentary by 4 skeptical primary care physicians