THE
2023-24

Medical-Dental-Legal UPDATE

Medical Malpractice • Risk Management • Practice Management
Healthcare Law • Selected Clinical Topics

American Educational Institute, Inc.

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David R. Victor, JD
CEO

Dear Registrant:

You practice in a dynamic and challenging environment. While keeping clinically current is imperative, it isn't enough. You must also acquire the skills necessary to navigate a professional liability minefield, manage a more effective and efficient practice, and master a maze of healthcare laws and regulations. ***The 2023-24 Medical-Dental-Legal Update*** is designed to assist you in that endeavor.

In one course you will receive 20 hours of vital instruction from national experts in the fields of law, medicine, public health, accounting, insurance, asset protection, pharmacology, and practice management. And their presentations include topics ranging from minimizing liability exposure, malpractice litigation, fraud and abuse, and financial literacy, to gynecology screening, new drugs and guidelines, vaccine schedules, ADHD, obesity, and diabetes.

To help you assess your level of comprehension we offer brief self-evaluations that may be taken either before or after the presentations concerned. These tests are included in this syllabus and are identified by the black edges of the pages on which they are featured.

As always, I am very interested in your reaction to this year's presentation. Please do me the favor of taking the time to complete the evaluation questions presented on screen for each presentation. In addition, I encourage you to contact any of our faculty members directly with questions or comments.

Finally, I urge you to take advantage of the diversity of professionals enrolled this week. Chances are your classmates include physicians, dentists, and attorneys. What better way to gain another perspective on these multi-faceted issues than to discuss them with a colleague from a different discipline.

Thank you for your participation and please accept my best wishes for a safe, enjoyable and enlightening visit.

Cordially,
American Educational Institute, Inc

David R. Victor, Esq
Chief Executive Officer

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Medical-Dental-Legal UPDATE

COURSE OBJECTIVES

After completing ***The 2023-24 Medical-Dental-Legal*** Update you should have acquired the knowledge that will better enable you to better:

- Utilize techniques for **better communication** with patients and staff
- Identify **gynecological screening** options and when they are appropriately administered
- Understand and advise on the **sexual health of older patients**
- Understand the elements and impact of **medical malpractice litigation**
- Understand and avoid running afoul of federal **Fraud & Abuse** laws and regulations
- Discuss **immunization updates and new FDA drug approvals** and safety guidelines
- Discuss ways to maximize **asset protection and tax efficiency**
- Utilize a variety of **clinically relevant but relatively unknown treatments**
- Identify current ADA-endorsed goals for treatment of **type 2 diabetes**
- Understand the nature, implications, and management of **obesity**
- Identify screening and treatment tools for **childhood and adult ADHD**
- Identify **asset protection** structures and strategies
- Identify **insurance gaps and litigation stress** management techniques
- Understand the nature and impact of current **childhood and adolescent vaccination schedules**
- Understand **adult vaccine recommendations**
- Discuss the characteristics and proper management of patients with current or past **substance use disorder.**

All learning objectives above address IOM/ACGME core competencies.

THE 2023-24

Medical-Dental-Legal UPDATE

FACULTY DISCLOSURES

The individuals listed below have control over the content of ***The 2023-24 Medical-Dental-Legal Update***. None of them have a financial relationship with a commercial interest whose product or services are discussed in the presentation(s) over which they have control:

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Louis Kuritzky, MD. Of Gainesville, Florida, is a board-certified, family practitioner and a certified Specialist in Hypertension with the American Society of Hypertension. He is clinical faculty at the UCF/HCA Family Medicine Residency Program in Gainesville and a clinical assistant professor emeritus at the University of Florida.

Dr. Kuritzky has given over 1,000 presentations to national and international medical audiences on dozens of clinical topics and has authored over 150 articles in journals including *New England Journal of Medicine*, *JAMA*, *Comprehensive Therapy*, *Hospital Practice*, *Consultant*, *Postgraduate Medicine*, *Journal of Pain and Palliative Care*, and *Patient Care*.

You may contact Dr. Kuritzky with any questions or comments at (352) 377–3193 or by email at lkuritzky@aol.com.

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Things I Wish I Knew Last Year

Presentation Process

- Questions/comments after EACH segment
- I will ask
  - Yea
  - Nay
- Can I contribute
  - Scientific Rigor
  - Recognition in Presentation
- All items referenced

Case: A Migraine Patient with CMI

A 21 y.o. graduate student reports that NSAIDs as migraine abortives provide some results for her migraine with aura, but not triptans. She wants to know if there are other inexpensive migraine agents she might try. An evidence-based choice might be

A) A parenteral CGRP-inhibitor (e.g., evolocumab)

B) A oral CGRP-inhibitor (e.g., ubrogepant)

C) An ophthalmic beta blocker (e.g., timolol)

D) An oral 'ditan' (e.g., lasmiditan)

Research

JAMA Ophthalmology | Original Investigation

Short-term Efficacy and Safety of Topical β-Blockers (Timolol Maleate Ophthalmic Solution, 0.5%) in Acute Migraine
A Randomized Crossover Trial

Abraham Kurian, MS, DO; Iodine Reghunadhan, DNB; Pratibha Thilak, MBBS, DNB; Indulekha Soman, MBBS, DNB; Unnikrishnan Nair, MS

Kurian A, et al *JAMA Ophthalmology* 2020;138(11):1160-1166

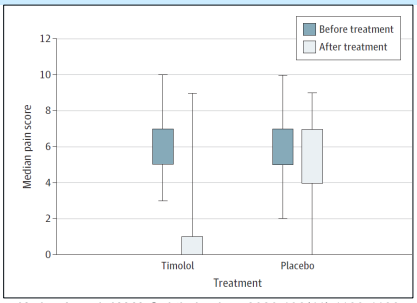
Migraine Abortive:
Ophthalmic Beta Blocker (timolol maleate 0.5%)

- Study: RDBPCXOT migraneurs (n=50)
- Rx (3 months with 1 month XO) :
  - timolol 0.5% ophthalmic solution 1gtt each eye at headache onset vs placebo (timolol vehicle)
  - may repeat at 10 mins
- Outcome: Pain score at 20 mins

Kurian A et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Migraine Abortive:
Ophthalmic Beta Blocker (timolol maleate 0.5%)

Headaches Treated =619



N = 50

Kurian A et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Migraine Abortive
Ophthalmic timolol maleate 0.5%: Metabolism

- Ophthalmic timolol bypasses 1st-pass hepatic metab
- Time to peak plasma level
  - Ophthalmic: peak at 10 mins (similar to IV bolus)
  - Oral timolol 20 mg: peak at 1-2 hours

Kurian A et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Migraine Abortive:
Ophthalmic Beta Blocker (timolol maleate 0.5%)

"This randomized XO trial supports consideration of timolol eyedrops in the acute Rx of migraine. Further research is warranted to determine if the improvements observed are sustained for a longer follow-up…."

Kurian A et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Case: Switching from Warfarin to a DOAC

A 72 y.o. man with atrial fibrillation has enjoyed excellent TTR with warfarin but finds it inconvenient to come in for INR checks and doesn't like the potential food restrictions and drug interactions of warfarin. He is considering a DOAC (e.g., rivaroxaban). Does he have to worry about any potential drug-drug interactions with a DOAC?

A) No, silly, that's why we like DOACs better than warfarin

B) Yes, but none have sufficient impact to cause any concern for risk

C) Yes, clinicians and patients need to be informed about potentially clinically relevant drug-drug interactions

COMMENTARY

THE AMERICAN JOURNAL of MEDICINE®

Drug-Drug Interactions with Direct Oral Anticoagulants: Practical Recommendations for Clinicians

Terrier J, et al *Am J Med* 2021;134(8):939-942

DOAC Drug-Drug Interactions

"In theory, DOACs do not require routine monitoring….Several large registry-based retrospective studies have also suggested an ↑ risk of bleeding when DOACs are co-administered with P-glycoprotein or P450 3A4/5 inhibitors."

Terrier J, et al *Am J Med* 2021;134(8):939-942

DOAC Drug-Drug Interactions

"…the strong CYP3A4/5 and Pgp/CYP3A4/5 inhibitors are the most likely to ↑ the DOACs AUC by a factor of 2 and put the patient at high risk for bleeding.

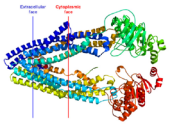
Terrier J, et al *Am J Med* 2021;134(8):939-942

DOAC Drug-Drug
Example Pgp or P450 3A4 **STRONG** Inhibitors

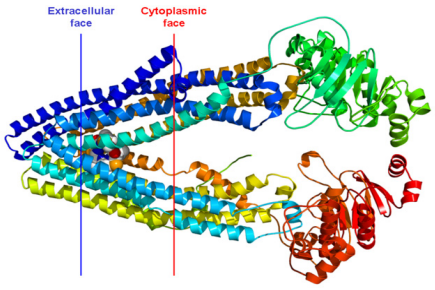
P450 3A4	P-GLYCOPROTEIN PUMP
CLARITHROMYCIN	AMIODARONE
ERYTHROMYCIN	AZITHROMYCIN
DRONEDARONE	CARVEDILOL
GRAPEFRUIT JUICE	QUINIDINE
ITRACONZAOLE	VERAPAMIL

UpTo Date accessed March 12, 2022

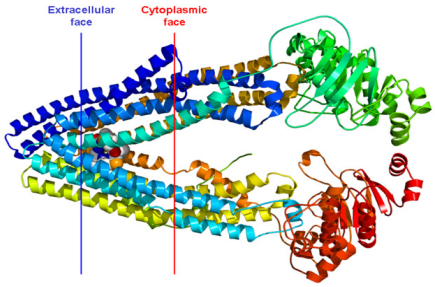
What's This?



How 'Bout If I Make It Bigger?



P-glycoprotein: Crystallographic Structure

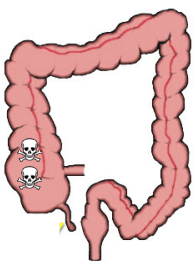


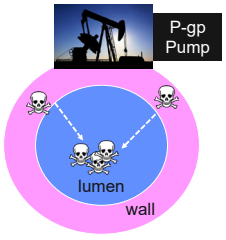
Wikipedia accessed 4/5/15

What is P-glycoprotein?

- P-gp = permeability glycoprotein
- Protein in cell membranes that pumps foreign substances out of cells
- Present in humans, animals, fungi, bacteria

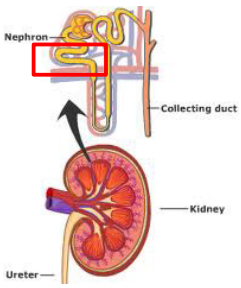
Wikipedia "P-glycoprotein" accessed 4/5/15

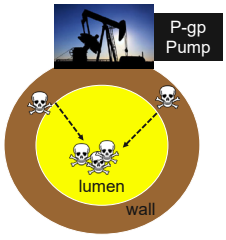




Intestinal X-Section

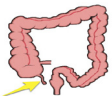
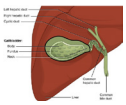
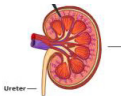
"P-gp is extensively distributed and expressed in the intestinal epithelium where it pumps xenobiotics (eg, toxins, drugs) back into the intestinal lumen…"
Wikipedia "P-glycoprotein" accessed 4/5/15





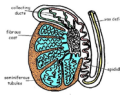
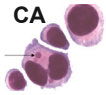
Proximal Tubule X-Section

"P-gp is extensively distributed…in the proximal tubule of the kidney where it pumps xenobiotics (eg, toxins, drugs) into urine conducting ducts…."
Wikipedia "P-glycoprotein" accessed 4/5/15

"P-gp is extensively distributed and expressed in the intestinal epithelium...in liver cells where it pumps…into bile ducts,…..kidney, ….in the capillary endothelial cells composing the blood-brain barrier and blood-testis barrier, where it pumps them back into the capillaries. Some cancer cells also express large amounts of P-gp, which renders cancers multi-drug resistant."

Wikipedia "P-glycoprotein" accessed 4/5/15

Case: Uncertainties About Penicillin

A 35 y.o. female (Centor 0) presents with Sx of sore throat x 3 days. She has tonsillar exudate (Centor +1), adenopathy (Centor +1), fever of 100.8 (Centor +1) and no cough (Centor +1). Her chart indicates 'PENICILLIN ALLERGY'. Your best next step

A) Rx: Quinolone

B) Rx: Erythromycin

C) Rx: Azithromycin

D) Get more information

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

What to Do With a Penicillin Allergy Hx

"A detailed Hx should be obtained directly from patients to determine their risk of penicillin allergy. Those deemed at low risk may not require a formal allergy evaluation."

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

Why Bother with a Penicillin Allergy Hx

"…more than 95% of hospitalized patients labeled as having penicillin allergy can actually tolerate this class of drug without adverse reactions."

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

Penicillin Allergy: Time Is Your Friend

- Post-reaction IgE levels wane over time, such that
  - At 10 years: 80% will tolerate
  - At 20 years: 99% will tolerate

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

Penicillin Allergy: PEN-FAST Screen

- PENicillin allergy reported: proceed with assessment
- Five years or less since a reaction, or unknown interval (2 pts)
- Anaphylaxis or angioedema or Severe cutaneous reaction (2 pts)
- Treatment was required for the episode (1 pt)

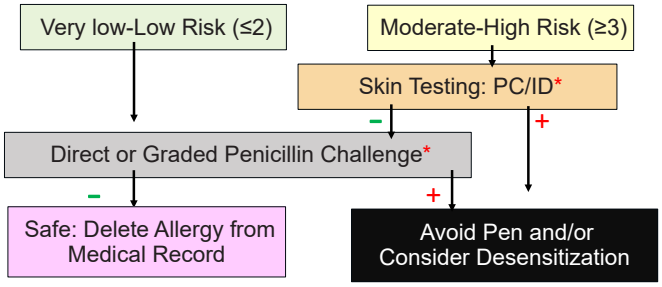
Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

PEN-FAST Screen Interpretation Likelihood of + Penicillin Allergy Skin Test

- 0: very low risk (<1%)
- 1-2: low risk (5%)
- 3: moderate risk (20%)
- 4-5: high risk (50%)
- 0-2: negative predictive value = 96.3%

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

Algorithm as per PEN-FAST Score



*Reactions excluding skin testing/challenge: Stevens Johnson, DRESS, Nephritis, Serum Sickness, hemolytic anemia

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

Penicillin Challenge: Adults

- Direct:
  - amoxicillin 250 mg p.o.
  - Observe 1-2 hrs.
- Graded:
  - Amoxicillin 25 mg
  - Wait 30-60 mins
  - Amoxicillin 225 mg
  - Observe 1-1.5 hrs.

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

PenFAST Utility

"The recently validated PEN-FAST penicillin allergy clinical decision rule may be useful for clinicians of all specialties to direct appropriate strategies, and for some patients, to potentially remove the 'penicillin allergy' label from their medical records."

Ohtola JA, Hong SJ *Cleveland Clin J Med* 2022;89(3):126-129

CASE: Problematic Facial Flushing

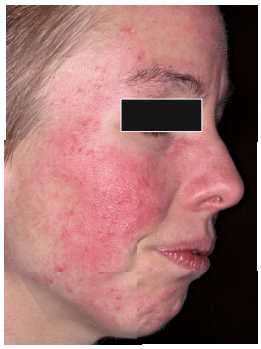
A 36 y.o. has failed multiple treatments to reduce facial flushing attributed to rosacea. She is frustrated that people keep inquiring about excessive alcohol intake, since she does not drink. She has failed multiple 'traditional' treatments. What might help?

a) Niacin (as nicotinic acid) 2 g daily p.o.

b) Nifedipine 60 mg po

c) She should stop lying about being a non-drinker & sober-up

d) Carvedilol p.o.



Habif TP Clinical Dermatology (6th Edition) 2016 Elsevier

Pronounced facial flushing and persistent erythema of rosacea effectively treated by carvedilol, a nonselective β-adrenergic blocker

Chia-Chi Hsu, MD, Julia Yu-Yun Lee, MD

Journal of the American Academy of Dermatology
LTE 2012;67(3):491-493

Erythemato**t**elangiectatic **R**osacea Endorsed Treatments

Severe Erythematotelangiectatic Rosacea

- B-Blockers
- Clonidine
- Naloxone
- Ondansetron
- Endoscopic Thoracic Sympathectomy

HSU CC, Lee *JYY J Am Acad Dermatol* 2012;67(3):491-492

ETR: Carvedilol Case Series

- Study: ETR Case series (n= 11)
- Based upon initial success in 1 case
- Previous Failed Rx with ≥1 of
  - Doxycycline
  - Corticosteroids
  - Propranolol
  - Clonidine
  - Metronidazole
  - Ondansetron
  - Tacrolimus/pimecrolimus
  - Thoracic sympathectomy
  - Stellate ganglion block
  - Pulsed dye laser

HSU CC, Lee JYY *J Am Acad Dermatol* 2012;67(3):491-492

ETR: Carvedilol Case Series

- Rx: carvedilol 3.125 mg/d → 31.25 mg/d divided b.i.d.-t.i.d. added to existing Rx x 1 yr
- Metrics:
  - Photo-based facial erythema
  - Cheek temperature
  - VAS 0-10 (pt assessment)

HSU CC, Lee JYY *J Am Acad Dermatol* 2012;67(3):491-492

ETR: Carvedilol Case Series Results

"All patients experienced significant clinical improvement within 3 weeks (range 3-21 days, mean 10.5 days)."

HSU CC, Lee JYY *J Am Acad Dermatol* 2012;67(3):491-492

ETR: Carvedilol Case Series Results

	Carvedilol
Cheek Temperature	↓2.2^0 C
VAS: Baseline VAS End of Rx	8.4/10 2.1/10

* Results are *MEAN*

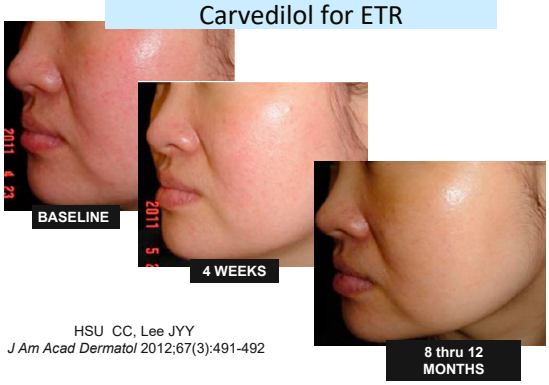
HSU CC, Lee JYY *J Am Acad Dermatol* 2012;67(3):491-492

ETR: Carvedilol Case Series Discussion

"Carvedilol appears special among β-blockers in its significant antioxidant and anti-inflammatory properties, which may explain its efficacy in treating ETR in the current study."

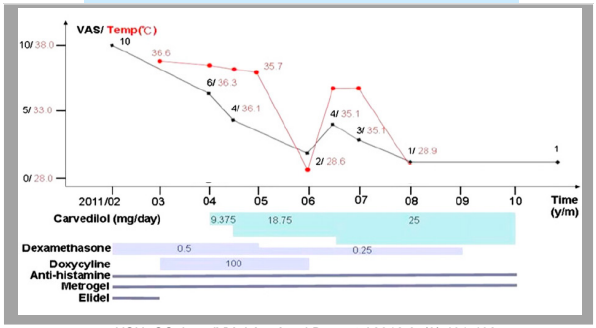
HSU CC, Lee JYY *J Am Acad Dermatol* 2012;67(3):491-492

Carvedilol for ETR



HSU CC, Lee JYY
J Am Acad Dermatol 2012;67(3):491-492

Carvedilol: Rosacea



HSU CC, Lee JYY *J Am Acad Dermatol* 2012;67(3):491-492

Topical timolol 0.5% gel-forming solution for erythema in rosacea: A quantitative, split-face, randomized, and rater-masked pilot clinical trial

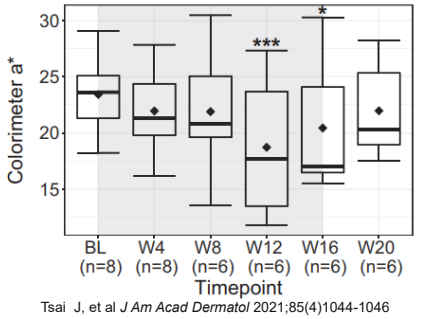
Research Letter:
Tsai J et al *J Am Acad Dermatol* 2021;85(4):1044-1046

Rosacea: Timolol 0.5% Solution

- Study: Rosacea with persistent flushing & erythema (n=8)
- Rx: Split-face timolol 0.5% gel-forming solution b.i.d. x 16 weeks
- Facial Erythema Metrics
  - Tri-stimulus colorimetry
  - Computer-aided image analysis

Tsai J, et al *J Am Acad Dermatol* 2021;85(4)1044-1046

Rosacea Erythema Score
Timolol 0.5% Topical X 16 weeks



Tsai J, et al *J Am Acad Dermatol* 2021;85(4)1044-1046

Rosacea: Timolol 0.5% Solution
Additional Observations

- No dropouts due to adverse effects
- Tolerance?: erythema uptick week 12-16
  - Seen in timolol Rx of glaucoma
  - Remedy (glaucoma): Rx hiatus + alpha agonist (brimonidine)
- Rebound?

Tsai J, et al *J Am Acad Dermatol* 2021;85(4)1044-1046

CASE: Stress Incontinence

A 46 y.o. G3P3 woman reports distressing loss of urine upon coughing, sneezing, and exertional activities like running or jumping. She does not have urgency or frequency. Because of being uninsured, she cannot access formal pelvic floor training/physical therapy. What Rx might help?

A) Duloxetine 40 mg b.i.d.

B) Riboflavin 400 mg qd

C) Tamsulosin 0.4 mg qd

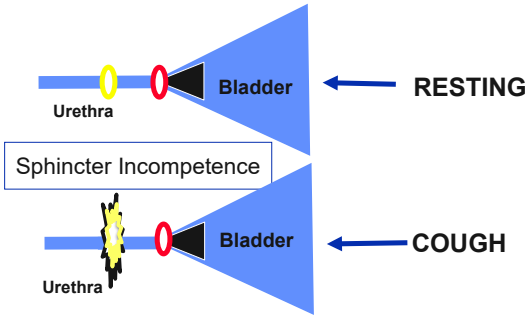
D) St. John's Wort (hypericum) 300 mg t.i.d.

BJOG: an International Journal of Obstetrics and Gynaecology
March 2004, Vol. 111, pp. 249–257
DOI: 10.1111/j.1471-0528.2004.00067.x

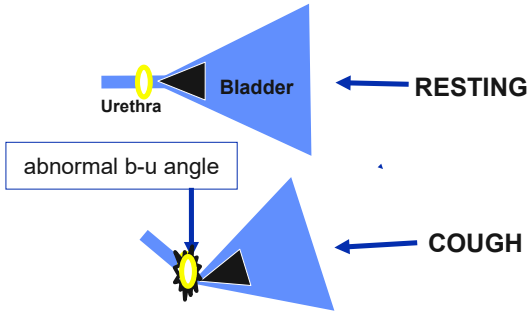
Duloxetine *versus* placebo in the treatment of European and Canadian women with stress urinary incontinence

Van Kerrebroeck *Brit J Obstet Gynaecol* 2004;111:249-257

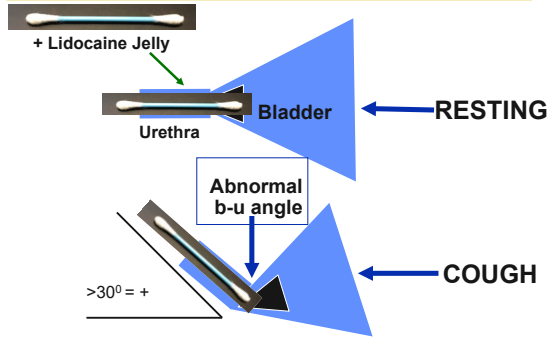
Stress Incontinence
External Sphincter Incompetence



Stress Incontinence
Pelvic Floor Deficits



Stress Incontinence: Q-Tip Test



Non-Pharmacologic Rx

Stress Incontinence

- Kegel Exercises
  - 10 reps 10 seconds Q.i.D. x 8 weeks
- Biofeedback
- Vaginal cones
- Pessary
- Urethral devices

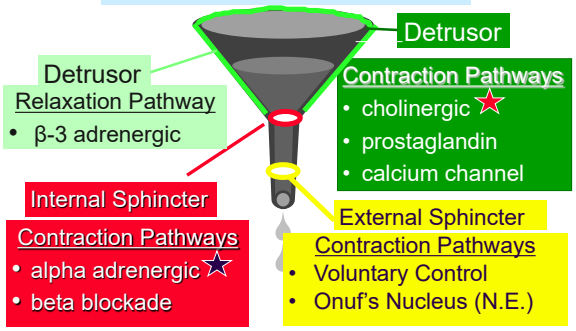
Bartholomew D "Urinary Incontinence" *Conn's Current Therapy*, Rakel, Bope eds, Elsevier Science (Philadelphia) 2003:744-748

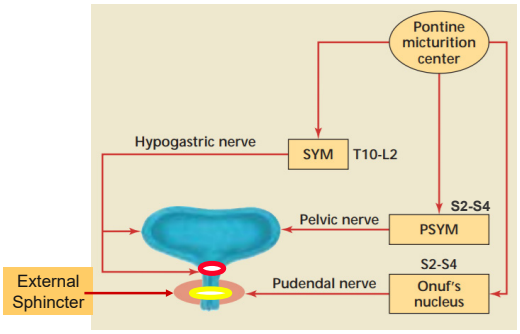
BJOG: an International Journal of Obstetrics and Gynaecology
March 2004, Vol. 111, pp. 249–257
DOI: 10.1111/j.1471-0528.2004.00067.x

Duloxetine *versus* placebo in the treatment of European and Canadian women with stress urinary incontinence

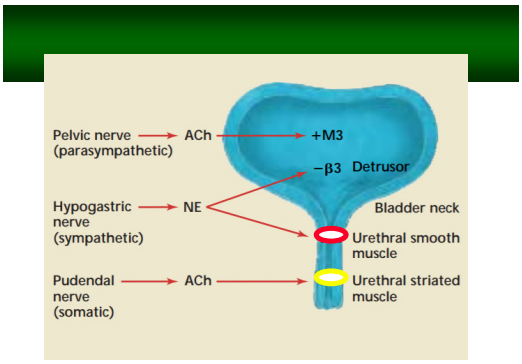
Van Kerrebroeck *Brit J Obstet Gynaecol* 2004;111:249-257

ABC's of Incontinence



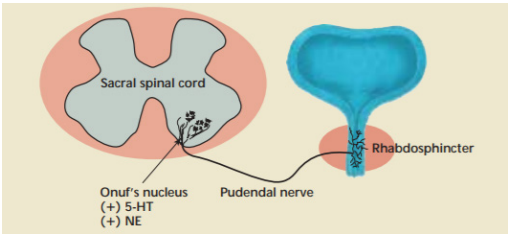


Sweeney DD, Chancellor MB *Rev Urol* 2005;7(2):81-86



Sweeney DD, Chancellor MB *Rev Urol* 2005;7(2):81-86

Stress Incontinence: Onuf's Nucleus



Sweeney DD, Chancellor MB *Rev Urol* 2005;7(2):81-86

Stress Incontinence: Duloxetine

- Study: RDBPCT Stress Incontinence (n=494)
- Inclusion
  - Incontinence ≥ 7/wk
  - No Urge Sx
  - Bladder capacity ≥ 400ml
- Rx: duloxetine 40 mg b.i.d. X 12 weeks
- Outcomes:
  - Incontinence episodes
  - QOL

van Kerrebroeck *Brit J Obstet Gynaecol* 2004;111:249-257

Stress Incontinence: Duloxetine

	Incontinence Episodes/week			
	Placebo	%Δ median	Duloxetine 40 mg bid	%Δ median
Baseline	14		13	
4 weeks	11	20.0%	6.6	53.6%
8 weeks	9.0	29.8%	7.0	53.9%
12 weeks	9.1	28.6%	7.0	51.8%

*p <0.05 all time points

van Kerrebroeck *Brit J Obstet Gynaecol* 2004;111:249-257

CASE: Knee Arthritis

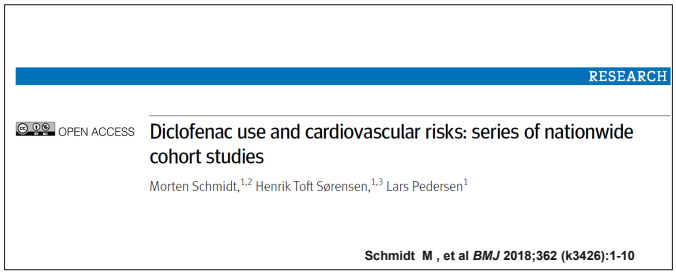
A 66 y.o. obese man takes NSAIDs for his knee arthritis 3-4 per week. His wife recently read some concerning information about CV risks of NSAIDS. Is one NSAID better/worse than another for CV risk, or is it NSAID/SchmedSAID?

A) Ibuprofen has the highest risk

B) Meloxicam has the highest risk

C) Diclofenac has the highest risk

D) Naproxen has the highest risk



NSAIDS & CV Risk

- Study: NSAID use in Denmark (1996-2016) in relation to CV Events
- Inclusion (adult new Rx users)
  - Diclofenac (= 1,370,832)
  - Ibuprofen (n = 3,878,454)
  - Naproxen (n = 291,490)
  - Acetaminophen [aka paracetamol] (n= 761,781)
- Major CV events within 30 days of initiation

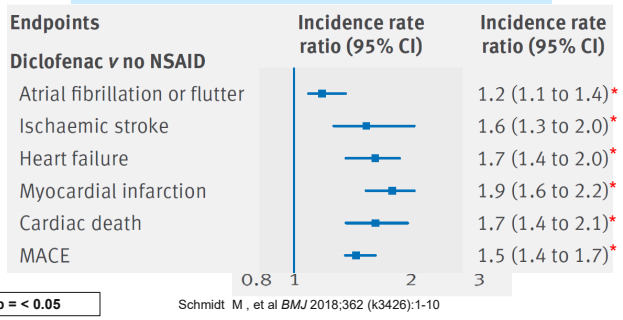
Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

NSAIDS & CV Risk
Maybe Some Surprises?

"…The relative risk of major adverse CV events was highest in individuals with low or moderate baseline risk…."

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

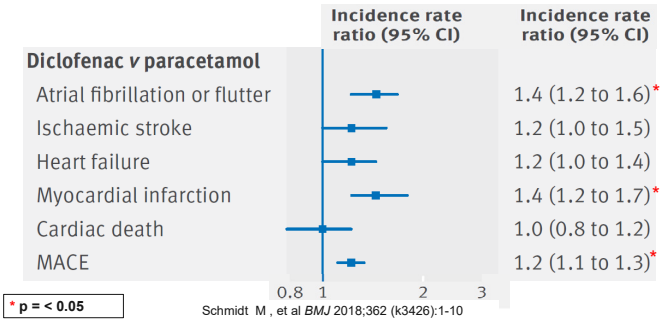
Diclofenac vs No NSAID: CV Risk



* p = < 0.05

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

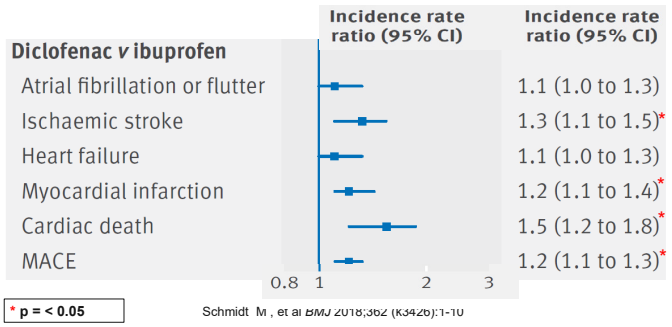
Diclofenac vs Acetaminophen: CV Risk



* p = < 0.05

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

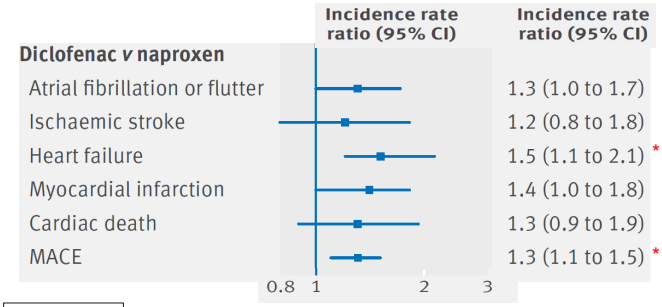
Diclofenac vs Ibuprofen: CV Risk



* p = < 0.05

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

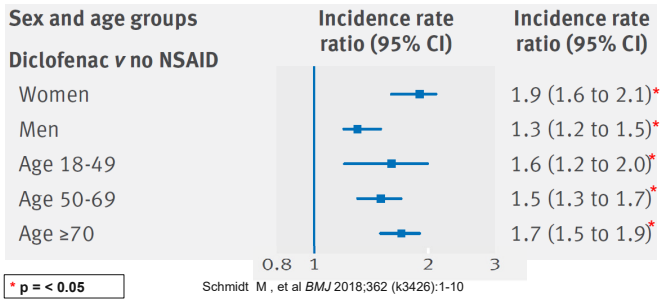
Diclofenac vs Naproxen: CV Risk



* p = < 0.05

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

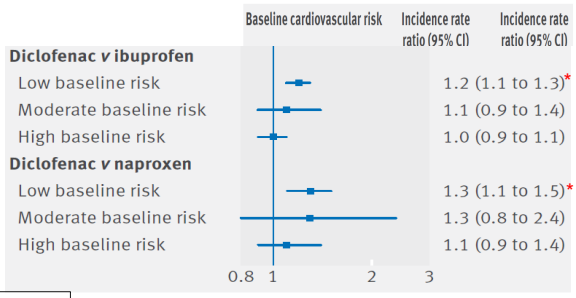
Diclofenac vs No NSAID: CV Risk Age/Gender Subgroups



* p = < 0.05

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

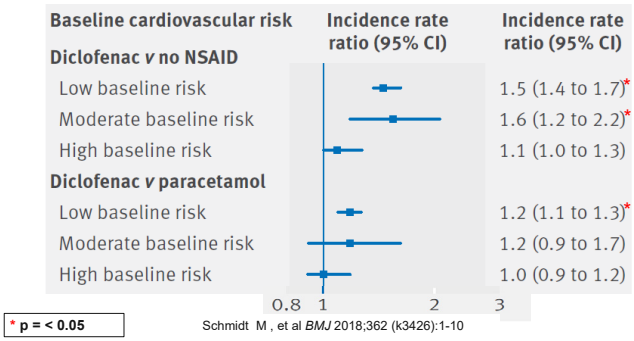
Diclofenac CV Risk by Baseline Risk Status



* p = < 0.05

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

Diclofenac CV Risk by Baseline Risk Status



* p = < 0.05

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

NSAIDS & CV Risk: Conclusions

"Treatment of pain and inflammation with NSAIDS may be worthwhile for some patients to improve QOL despite potential side effects. Considering its CV and GI risk, however, there is little justification to initiate diclofenac Rx before other traditional NSAIDs."

Schmidt M , et al *BMJ* 2018;362 (k3426):1-10

CASE: Alcohol Withdrawal

A 36 y.o. chronic alcoholic, with numerous previous alcohol detox admissions, stopped drinking this morning, but is unwilling to be admitted for detox because he has exhausted his insurance coverage. Which of the following might be helpful?

A) methylphenidate
B) baclofen
C) saw palmetto
D) tiotropium

Managing Alcohol Withdrawal in an Outpatient Setting

- PREMISES:
  - AWD psychologically and physically taxing
  - Sx begin 6-24 hrs. after last drink
  - Typical Sx = HTN, tachycardia, tremor, hyperreflexia, anxiety, seizures, delirium
  - benzodiazepines are mainstay of Rx

Addolorato G et al, *Am J Med* 2002;112 (Feb 15):226-229

Managing Alcohol Withdrawal in an Outpatient Setting

- GOALS:
  - Sx relief
  - Seizure prevention
  - Smooth transition to long-term abstinence

Addolorato G et al, *Am J Med* 2002;112 (Feb 15):226-229

Managing Alcohol Withdrawal in an Outpatient Setting

- BACKGROUND: baclofen
  - ↓ alcohol craving and intake during cessation program
  - suppressed withdrawal syndrome in physically dependent rats
  - animal studies : ↓ voluntary alcohol intake in habituated rats

Addolorato G et al, *Am J Med* 2002;112 (Feb 15):226-229

Managing Alcohol Withdrawal in an Outpatient Setting

- STUDY: 5 alcohol-dependent (16-35 drinks daily X 3-9 years) pts beginning cessation
- INCLUSION: Clinical Institute Withdrawal Assessment for Alcohol Scale >20 (= severe withdrawal)
- Rx: 10 mg baclofen Q8H X 30 days (caretaker)
- MONITORING: Withdrawal scale Q1H X 4-8 hrs, then QD X 7 days

Addolorato G et al, *Am J Med* 2002;112 (Feb 15):226-229

Managing Alcohol Withdrawal in an Outpatient Setting

"A single administration of 10 mg baclofen… resulted in rapid disappearance of alcohol withdrawal Sx in all patients. Throughout the 30-day follow-up, all patients were aSx and abstained from alcohol"

Addolorato G et al, *Am J Med* 2002;112 (Feb 15):226-229

Baclofen for Alcohol Withdrawal: Pt #1

- Immediate preRx Withdrawal score = 34: paroxysmal sweats, tremor, anxiety, agitation, tactile disturbances, headache
- Pulse =108, BP 185/90
- Post 1st dose 30 mins : Sx ↓
- 60 mins: total Sx resolution (withdrawal score = 0), pulse = 85, BP = 150/70 maintained Q1H x 6 → home
- Withdrawal score = 0 each subsequent visit

Addolorato G et al, *Am J Med* 2002;112 (Feb 15):226-229

Baclofen for Alcohol Withdrawal: Pt #2

- Immediate preRx Withdrawal Score = 23: nausea, paroxysmal sweats, vomiting, tremor, anxiety, agitation, tactile disturbances, visual disturbances
- Pulse = 95, BP 145/90
- Post 1st dose 60 mins : withdrawal score = 21
- 120 mins: score = 8, pulse = 80, BP = 130/70
- 180 mins: withdrawal score = 0 → home at 8 hours
- All subsequent f/u visits withdrawal score = 0

Addolorato G et al, *Am J Med* 2002;112 (Feb 15):226-229

Research

JAMA | Original Investigation

Association of Baclofen With Encephalopathy in Patients With Chronic Kidney Disease

Muanda FT, et al *JAMA* 2019;322(20):1987-1995

Baclofen: Relative Risk of Encephalopathy

- Study: compare rates of hospitalization for encephalopathy in CKD patients within 30 days of new baclofen Rx (Ontario, Canada)
  - ≤20 mg/d (n=6,235) vs >20 mg/d (n=9,707)
  - vs Non-users (n = 284,263)
- Inclusion
  - Age ≥ 66 (median = 77)
  - GFR <60 ml/min (mean = 47)
- 1^0 Outcome: Encephalopathy hospitalization

Muanda FT, et al *JAMA* 2019;322(20):1987-1995

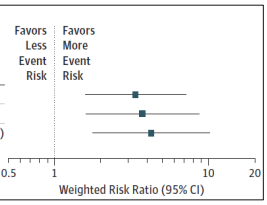
Baclofen: Relative Risk of Encephalopathy

Baclofen Status	RR Encephalopathy ≤30d	%
Non-user	1	0.06%
Baclofen <20 mg/d	5.90 (3.59-9.70)	0.11%
Baclofen >20 mg/d	19.8 (14.0-28.0	0.42%

Muanda FT, et al *JAMA* 2019;322(20):1987-1995

Baclofen & Encephalopathy As Per CKD Stage

Baseline eGFR, mL/min/1.73 m²	No. of Encephalopathy Events/ Total No. of Patients at Risk (%) Baclofen ≥20 mg/d	Baclofen <20 mg/d	Weighted Risk Ratio (95% CI)
45-59	38/6404 (0.59)	11/6383 (0.18)	3.37 (1.58-7.21)
30-44	44/2616 (1.68)	12/2617 (0.45)	3.74 (1.60-8.78)
<30	26/687 (3.78)	6/681 (0.89)	4.26 (1.77-10.25)



Muanda FT, et al *JAMA* 2019;322(20):1987-1995

Baclofen: FDA Labeling (2022) Contraindications/Precautions

"Cases of baclofen toxicity (manifesting as encephalopathy, abdominal pain, and in some cases, seizures and respiratory depression) have been reported in patients with severe renal impairment (e.g., serum creatinine >2 mg/dL)….."

Muanda FT, et al *JAMA* 2019;322(20):1987-1995

Baclofen: FDA Labeling (2022) **Contraindications/Precautions**

"Most patients who became toxic received low oral does of baclofen (e.g., 15-30 mg/d) for a short duration."

Muanda FT, et al *JAMA* 2019;322(20):1987-1995

CASE: Non-Pharmacologic HTN Rx

A 60 y.o. woman has been recently diagnosed with HTN (150/92). Her BMI is 19.8, and she takes no medications, and would rather not take any. Which simple intervention might provide BP reduction for her?

A) 2 grapefruit daily (or 16 oz juice)
B) 3 oranges daily (or 18 oz juice)
C) 3 apples daily (or 18 oz juice)
D) 1 cup blueberries daily (or 22g freeze dried powder)

Blueberries for HTN Control: Premise

- Berries (high in polyphenols) → ↓ BP, ↓arterial stiffness
- Pilot trial suggested BP improvement
- Putative MOA
  - Polyphenols → NADPH oxidase inhibition → N.O. (nitric oxide) bioavailability → vasodilation

Johnson SA, et al *J Acad Nutrit Dietetics* 2015;115:369-377

Blueberries for HTN Control

- Study: RDBPCT PMP women (n=48)
- Inclusion: seated BP 125/85-160/90 mm Hg
- Rx: 22g freeze-dried blueberry powder (= 1 cup fresh blueberries) vs placebo x 8 weeks
- Outcomes:
  - SBP
  - DBP
  - Pulse-wave velocity (for arterial stiffness)

Johnson SA, et al *J Acad Nutrit Dietetics* 2015;115:369-377

Blueberries for HTN Control

	BLUEBERRIES		CONTROL	
	Baseline	8 weeks	Baseline	8 weeks
SBP (mm Hg)	138	131*	138	139
DBP (mm Hg)	80	75*	78	80
Pulse wave velocity (cm/sec)	1,498	1,401	1,470	1,477
CRP (mg/mL)	2.49	2.3	2.69	2.29
Nitric Oxide (mmol/L)	9.11	15.35*	9.81	10.73

* $p < 0.05$

Johnson SA, et al *J Acad Nutrit Dietetics* 2015;115:369-377

Blueberries for HTN Control: Conclusion

"Blueberry consumption may help in reducing both SBP and DBP and improving arterial stiffness in postmenopausal women with pre-and stage 1-HTN, in part, through increasing the production of nitric oxide and its vasodilatory effect."

Johnson SA, et al *J Acad Nutrit Dietetics* 2015;115:369-377

The Ever-Discerning Crucible of Science


RESEARCH

OPEN ACCESS

Check for updates

Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

Robert W Yeh,[1] Linda R Valsdottir,[1] Michael W Yeh,[2] Changyu Shen,[1] Daniel B Kramer,[1] Jordan B Strom,[1] Eric A Secemsky,[1] Joanne L Healy,[1] Robert M Domeier,[3] Dhruv S Kazi,[1] Brahmajee K Nallamothu[4] On behalf of the PARACHUTE Investigators

Yeh RW et al *BMJ* 2018;363(k5094):1-6

ABSTRACT

OBJECTIVE

To determine if using a parachute prevents death or major traumatic injury when jumping from an aircraft

DESIGN

Randomized controlled trial

SETTING

Private or commercial aircraft between September 2017 and August 2018

PARTICIPANTS

92 aircraft passengers aged 18 and over were screened for participation. 23 agreed to be enrolled and were randomized

INTERVENTION

Jumping from an aircraft (airplane or helicopter) with a parachute versus an empty backpack (unblinded)

Yeh RW et al *BMJ* 2018;363(k5094):1-6

INTERVENTION

Jumping from an aircraft (airplane or helicopter) with a parachute versus an empty backpack (unblinded).

MAIN OUTCOME MEASURES

Composite of death or major traumatic injury (defined by an Injury Severity Score over 15) upon impact with the ground measured immediately after landing.

RESULTS

?

Yeh RW et al BMJ 2018;363(k5094):1-6

Fig 2 Representative study participant jumping from aircraft with an empty backpack. This individual did not incur death or major injury upon impact with the ground

Yeh RW et al *BMJ* 2018;363(k5094):1-6

Fig 2 Representative study participant jumping from aircraft with an empty backpack. This individual did not incur death or major injury upon impact with the ground

Yeh RW et al BMJ 2018;363(k5094):1-6

INTERVENTION

Jumping from an aircraft (airplane or helicopter) with a parachute versus an empty backpack (unblinded).

MAIN OUTCOME MEASURES

Composite of death or major traumatic injury (defined by an Injury Severity Score over 15) upon impact with the ground measured immediately after landing.

RESULTS

Parachute use did not significantly reduce death or major injury (0% for parachute *v* 0% for control; P>0.9). This finding was consistent across multiple subgroups. Compared with individuals screened but

Yeh RW et al BMJ 2018;363(k5094):1-6

WHAT IS ALREADY KNOWN ON THIS TOPIC

Parachutes are routinely used to prevent death or major traumatic injury among individuals jumping from aircraft, but their efficacy is based primarily on biological plausibility and expert opinion

No randomized controlled trials of parachute use have yet been attempted, presumably owing to a lack of equipoise

WHAT THIS STUDY ADDS

This randomized trial of parachute use found no reduction in death or major injury compared with individuals jumping from aircraft with an empty backpack

Lack of enrolment of individuals at high risk could have influenced the results of the trial

Yeh RW et al BMJ 2018;363(k5094):1-6

SELF EVALUATION

Things I Wish I Knew Last Year

1. A 21 y.o. graduate student reports a partial favorable response to NSAIDs as migraine abortives, but not triptans. She wants to know if there are other INEXPENSIVE migraine abortive agents she might try. An evidence-based choice might be
    a. A parenteral CGRP-inhibitor (e.g., erenumab)
    b. A oral CGRP-inhibitor (e.g., ubrogepant)
    c. An ophthalmic beta blocker (e.g., timolol)
    d. An oral 'ditan' (e.g., lasmiditan)

2. A 72 y.o. man with atrial fibrillation has enjoyed excellent TTR with warfarin, but finds it inconvenient to come in for INR checks, and doesn't like the potential food restrictions and drug interactions of warfarin. He is considering a DOAC (e.g., rivaroxaban). Does he have to worry about any potential drug-drug interactions with a DOAC?
    a. No, silly, that's why we like DOACs better than warfarin
    b. Yes, but none have sufficient impact to cause any concern for risk
    c. Yes, clinicians and patients need to be informed about potentially clinically relevant drug-drug interactions

3. An otherwise healthy 40 y.o. man has been diagnosed with group A strep pharyngitis. At age 16 he received oral penicillin, also for strep pharyngitis, after which he briefly had a mild non pruritic rash that resolved without treatment within 48 hrs. Based on this history alone, what can you tell the patient about the likelihood that he will tolerate penicillin without adversity to treat the current streptococcal infection?
    a. Because of his reaction in adolescence he should never again receive penicillin
    b. Because of the 20 year interval, his likelihood of a significant penicillin adverse reaction is <1%
    c. Based on his history, you suggest prompt penicillin desensitization

4. A 50 y.o.woman complains of stress incontinence. Kegel exercises and pelvic floor strengthening as prescribed by a physical therapist have provided improvements, but she asks if there are pharmacologic agents that might help. She does NOT have urgency. What agent might be effective to treat her stress incontinence
    a. A muscle relaxant (e.g., cyclobenzaprine)
    b. A gabapentinoid (e.g., gabapentin)
    c. An SNRI (e.g., duloxetine)

5. Which NSAID has been demonstrated to have increased CVD risk compared to other agents in the same pharmacologic class?
    a. Diclofenac
    b. Ibuprofen
    c. Meloxicam

Answer Key: 1. C, 2. C, 3. B, 4. C, 5. A

David B. Mandell, JD, MBA

David B. Mandell, JD, MBA, of Ft. Lauderdale, Florida, is a practicing attorney in The Law Offices of David B. Mandell, PC and a principal of the wealth management firm OJM Group, LLC. He specializes in risk management, asset protection, and financial planning and has authored a number of books for doctors including, *Wealth Planning for the Modern Physician: Residency to Retirement*. Mr. Mandell also created the Category 1 CME monograph, *Risk Management for the Practicing Physician*. His articles have appeared in over 100 publications, including over 30 medical specialty journals, and he has addressed many of the nation's leading medical conferences.

Mr. Mandell holds a bachelor's degree from Harvard University from which he graduated with honors, a law degree from the UCLA School of Law where he was awarded the "American Jurisprudence Award" for achievement in legal ethics and earned his MBA from UCLA'S Anderson School of Management.

You may contact Mr. Mandell with any questions or comments at (877) 656–4362 or by email at mandell@ojmgroup.com.

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Protecting Professional and Personal Assets

David B. Mandell, JD, MBA

TODAY'S PRESENTATION

1. Background on physician financial stress
2. Asset protection fundamentals
3. Growing source of liability – qualified plans
4. Shielding physicians' & dentists' personal assets
5. Recent cases

PHYSICIANS STRESSED ABOUT LIABILITY

- 87 percent of respondents said they are moderately-to-severely stressed/burned out on an average day.*
- Concern about liability and lawsuits are a motivating force behind the skyrocketing costs associated with "defensive medicine"**
- 2016 PubMed study: "Exploring Physicians' Dissatisfaction and Work-Related Stress: Development of the PhyDis Scale"

*Of 2,000 physicians as reports by Bouchard, Stephanie, "Impact of Physician Stress Underestimated," *HealthCare Finance News*, December 2, 2011

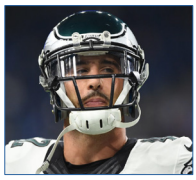
**Peter Ubel, "Do Malpractice Fears Cause Physicians To Order Unnecessary Tests?" Forbes.com, October 22, 2013

IN THE NEWS

CNN Sports

Former Philadelphia Eagles captain Chris Maragos Awarded $43.5 million in medical malpractice case

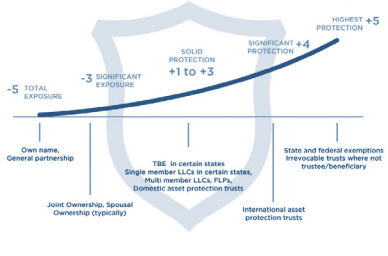
- February 15, 2023



TYPES OF LIABILITY FACING PHYSICIANS & DENTISTS

- Medical/dental malpractice
- Employer liability
  - Sexual harassment ("hostile work environment"); Wrongful termination (protected classes); Violation of fiduciary duty (qualified plans)
- Billing issues
  - Over-billing, improper billing, fraud, violation of anti-kickback rules, Stark rules, etc.
- HIPAA
- Premises liability
- Personal liability

ASSET PROTECTION "SLIDING SCALE"



*The scale presumes tools are created and utilized properly and when fraudulent transfer rules will not apply.

BEST ASSET PROTECTION NOT AP

- Why wealth protection MUST be tied to wealth creation: timing
- Like tax planning: economic substance
- Top (+5) tools are primarily not AP tools
- AP must be implemented in a multidisciplinary approach

PRACTICE/ANCILLARIES PROTECTION

- Insurances
- Choice of entity
- LLC lease-backs
- Qualified retirement plans
- Non-qualified plans
- Advanced tools

INSURANCES AS FRONT-LINE PROTECTORS

- Types of policies
  - Medical or dental malpractice
  - General Liability
  - Cyber
  - Landlord
  - Other
- Be aware of coverage limitations, deductibles
- Review and get second opinions

PROTECTING EQUIPMENT & REAL ESTATE

MAXIMIZE PROTECTIVE BENEFIT PLANS

- **Shields #1 asset – cash flow**
- Qualified retirement plans (QRPs): state exemption laws vary
  - Most states also protect QRPs to an unlimited value
  - Some states: value limitations
  - Some states: timing claw-backs
- Non-qualified plans – depends on funding mechanism
  - COLI – about 20 states provide (+5) exemption
  - Other states: can use trusts or LLCs

ARE YOU EXPOSED?

- Parties involved in QRP administration
  - Recordkeeper
  - Third Party Administrator
  - Investment advisor
- "Bundled" services often lead to conflicts, kick-backs, expensive fund lineups
- Many small practice plans have not been reviewed
- As plan sponsor/trustee, you have fiduciary liability to employees
  - You can be sued for underperformance; high expense funds
    - U. of Chicago, MIT
    - MassMutual, Ameriprise, Nationwide settlements. Goldman Sachs ongoing
  - **Solution: have your plan audited independently with benchmarks**

CASE STUDY: SOLO SURGEON OVERPAYING AND EXPOSED

- Employees: 1 physician, 4 employees, including spouse
- Fees: 1.50% Investment Advisory
  - 2.41% across mutual fund expenses, TPA/Recordkeeping, and Investment Advisory
- This was a pooled investment account, meaning all participant investments are managed in the same manner. This can cause liability for the plan since not all participants will be comfortable taking the same level of risk.

Solution

- Plan design changed to allow each participant to direct his/her individual investments, including target-date retirement options.
- Per industry benchmarking, the advisory fee was dropped to 0.60% for the plan. Total fees dropped from 2.41% to 1.63%, which saved the plan $4,000 annually.

TITLING ASSETS: DOES IT PROTECT?

- Spousal
- Basics: Tenancy in common, joint tenancy
- Tenancy by the Entirety (TBE)
- Community Property

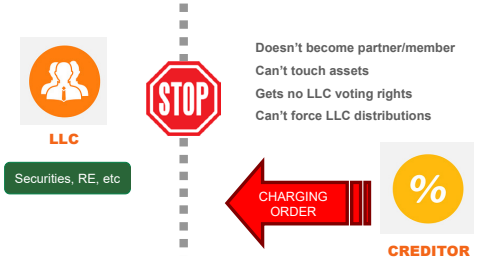
START WITH EXEMPT ASSETS (+5)

- (+5) Federal or state exempt asset
- No gifting, compliance, accounting fees or special taxes
- Protection cannot be matched by any other planning
- Federal bankruptcy exemptions for QRPs and IRAs
- States vary widely
  - Homestead
  - QRPs, IRAs
  - Life insurance and annuities

LLCs (+2): IDEAL FOR MOST ASSETS BEYOND EXEMPTIONS

- Inside Creditors
- Outside Creditors Isolates their lawsuit damage only to LLC property
  - Creditors can only get "charging order" against the LLC interest (+1 to +3) depending on use, compliance
  - Should tie into your estate plan
- "Building blocks" of asset protection
- *Control and Access*

WHAT A "CHARGING ORDER" MEANS

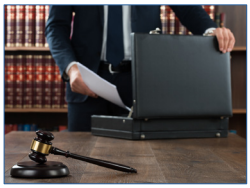


KEYS TO PROTECTION: LLCs

- Proper operating agreement
- Compliance with annual formalities
- Non-asset protection purpose: estate planning/gifting
- Jurisdiction: use the best state, when you have options
- Many LLCs are lacking in 1 of the 4 elements above: vulnerable
- Key: experienced attorney who has annual monitoring/gifting plan

USING TRUSTS TO SHIELD ASSETS

- Revocable trusts
  - "Family," "living," "loving trusts"
  - Valuable for probate avoidance, in event of incapacity
  - No asset protection while you are alive
- Irrevocable trusts
  - Many types, including ILITs, GRATs, CRTs and DAPTs
  - Because they are irrevocable, strong asset protection
  - **DAPT is most innovative, newest**
    - 20 states
    - "Hybrid" version for other states
    - Different than LLCs

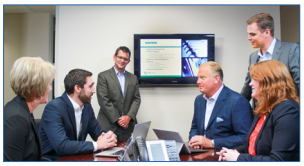


NEW CASES RELATED TO LLCS

- Reminder from last year's course: Excela Technologies
  - Delaware court allowed "reverse piercing" case vs. an LLC
- Two Ohio LLC cases
  - Wick v. Ash : Both trial and appellate court dismissed the "reverse piercing" claim
  - Berns Custom Homes v. Johnson : Court refuses to appoint receiver for LLC – charging order is the exclusive remedy for plaintiffs.
- IRS LLC Case
  - TBS Properties LLC v. United States: IRS attacks real estate-owning LLC for unpaid taxes owed by corporation lessee. Court allows case to move forward.
  - Formalities matter!

ABOUT OJM GROUP

- Unique, fee-based wealth management firm
- 1,000 physician clients in 48 states
- Multidisciplinary; three divisions
- Corporate and personal planning
- Goal: Reducing physician financial stress



HOW WE WORK WITH PHYSICIANS

- **Investing**
  - RIA
  - Fiduciary, independent custodian
  - Tax-focused
- **Insurance and Benefits**
  - Life, disability, long term care insurance
  - Through partner firm, P&C coverages
  - Qualified and non-qualified plans
- **Consulting**

PERSONAL WEALTH PLANNING

DIAGNOSTIC vs. TREATMENT

ADVICE & EXPERTISE FOR A FLAT FEE

BUILDING A RELATIONSHIP

OJMGROUP

NEXT STEPS TO LEARN MORE

- **Contact the presenter**
  - David B. Mandell, JD, MBA
  - 877.656.4362
  - mandell@ojmgroup.com
- **Free resources**
  - Text **AEIOJM** to 844-418-1212
  - Scan the QR Code
  - Visit ojmbookstore.com and enter **AEIOJM** at checkout.

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SELF EVALUATION

Protecting Professional and Personal Assets

1. According to the Healthcare Finance News survey referenced in the talk, the percentage of physicians surveyed who felt moderately-to-severely stressed was:

a. 17%
b. 37%
c. 47%
d. 87%

2. T/F - An orthopedic surgeon and practice were recently found liable for over $43 million in a malpractice claim.

3. Which of the following tools are generally used to shield practice real estate?

a. Limited liability companies (LLCs)
b. Community property
c. Spousal ownership
d. State or federally exempt assets

4. Which is a tool to shield cash flow at a practice:

a. Limited liability companies (LLCs)
b. Qualified retirement plans (QRPs)
c. Irrevocable trusts
d. Revocable trusts

5. T/F - Revocable trusts do not provide asset protection to you as the grantor while you are alive.

Answer Key: 1. D, 2. T, 3. A, 4. B, 5. T

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Caring for Patients with Current or Past Substance Use Disorder

DEFINITION

A cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state

World Health Organization. *International statistical classification of diseases and related health problems*

GOALS

- How do I treat a patient that is currently in medical assisted treatment for addiction (methadone or buprenorphine)?
- Will my treatment of this patient put them at risk for their sobriety?
- Will my treatment of this patient put them at risk for morbidity or mortality?
- How do I treat a patient with previous SUD if they are sober, off all medications?
- Can I be placed at fault if the patient relapses under my care?

CONCERNS

Patient concerns/fears

- Withdrawal symptoms
- Fear of pain not taken seriously restriction to analgesic agents
- Fear of discrimination
- If currently absent-fear of relapse

Physician concerns

- Mistrust of those with addiction
- overtreatment of pain leading to respiratory depression
- possibility reports of pain fabricated to obtain opiates
- diversion of prescription
- fear patient may leave against the medical advice

PRESENTATION

- There is a high prevalence of psychiatric comorbidities in those with drug dependence, with more than 50% of patients showing evidence of significant psychopathology, particularly anxiety disorders and affective disorders, including depression

Callaly T, Trauer T, Munro L, Whelan G. Prevalence of psychiatric disorder in a methadone maintenance population. *Aust N Z J Psychiatry* 2001;35:601–5

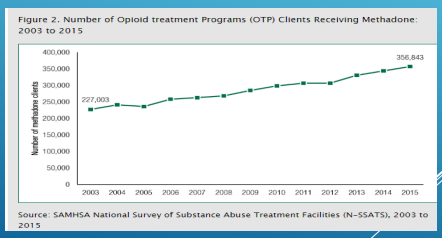
- Everyone is at risk.
- *Must the document* and appropriate history and physical exam.
- Must document risk assessment tool.
- Must actively engage patient with respect to medication risk and benefit.
- Must consider other therapies outside of narcotic management.

COMMON MISCONCEPTIONS

- The maintenance opioid agonist (methadone or buprenorphine)provides analgesia.
- Use of opioids for analgesia may result in addiction relapse
- The additive effects of opioid analgesics and OAT may cause respiratory/(CNS) depression.
- The pain complaint may be a manipulation to obtain opioid medications, or drug-seeking, because of opioid addiction.

TREATMENT- METHADONE

- Methadone- indeed block the euphoric effects of the heroin (and all other opioids).
- Prevents cravings/stabilize



METHADONE POSITIVES

- The goal -normal life-stop the withdrawal symptoms
- It lasts for at least 24 hours
- No legal limit to how many patients a methadone clinic can treat
- Increased as the patient becomes tolerant
- The addict can avoid withdrawal safely.
- Immediately stop using prevention hepatitis C and HIV.

https://www.adf-healthcare.com/blog/post/advantages-disadvantages-methadone-treatment
https://www.naabt.org/faq_answers.cfm?ID=21

LOW-RISK: STANDARD MONITORING, VIGILANCE, AND CARE

- Objective signs and symptoms, localizable physical pathology
- Confirmatory testing such as physical exam findings, CT, MRI, etc.
- No individual or family history of substance abuse
- At most, mild medical or psychologic comorbidity
- Age < 45
- High pain tolerance
- Active coping strategies
- Willingness to participate in multimodal therapy
- Attempting to function at normal levels

https://www.ncbi.nlm.nih.gov/books/NBK537318/#article-40661.s8

MODERATE-RISK: ADDITIONAL LEVEL OF MONITORING AND MORE FREQUENT PROVIDER CONTACT

- Significant pain
- Defined pathology with objective signs and symptoms
- Confirmatory testing such as physical exam findings, CT, MRI, etc.
- Moderate psychologic problems controlled by therapy
- Moderate comorbidities well controlled by medical therapy and are not affected by opioids
- Mild opioid tolerance but not hyperalgesia without addiction or physical dependence
- Individual or family history of substance abuse
- Pain involving more than three regions of the body
- Moderate levels of pain acceptance
- Active coping strategies
- Willing to participate in multimodal therapy
- Attempting to function at normal levels

https://www.ncbi.nlm.nih.gov/books/NBK537318/#article-40661.s8

HIGH-RISK: INTENSIVE AND STRUCTURED MONITORING, FREQUENT FOLLOW-UP CONTACT, CONSULTATION WITH ADDICTION PSYCHIATRIST

- Significant widespread pain
- No objective signs and symptoms
- Pain involves more than 3 body regions
- Divergent drug-related behavior
- Individual or family history of addiction, dependency, diversion, hyperalgesia, substance abuse, or tolerance
- Major psychologic problems
- Age >45
- HIV-related pain
- High levels of pain exacerbation
- Poor coping strategies
- Unwilling to participate in multimodal therapy
- Not functioning at a normal lifestyle

https://www.ncbi.nlm.nih.gov/books/NBK537318/#article-40661.s8

VIGIL

- Verification: Is this a responsible opioid user?
- Identification: Is the identity of this patient verifiable?
- Generalization: Do we agree on mutual responsibilities and expectations?
- Interpretation: Do I feel comfortable allowing this person to have controlled substances?
- Legalization: Am I acting legally and responsibly?

https://www.ncbi.nlm.nih.gov/books/NBK537318/#article-40661.s8

TREATMENT- METHADONE

- Treating Patients on this medication and Having Surgery
- What to do?
  Continue use?
  Decrease?
  Stop?
- How would/should I change my management of this patient?

PREOPERATIVE ASSESSMENT FOR THE OPIOID-TOLERANT PATIENT.

- Understand current opiate dose for sobriety maintenance
- Appreciate other polypharmacy patient might be taking
- Review past experiences with surgery and current expectations
- Focus on other modalities for pain relief/co-analgesic management

Patients who should receive pain consult: 1) Taking opioid equivalents oral morphine 80mg daily *(Morphine (MS-contin, morphine sulfate, MS-IR) – 80mg, Oxycodone (Percocet, oxycodone, Oxycontin) – 50mg, Hydrocodone (Norco, Vidocin, Zohydro ER) – 80mg, Hydromorphone (Dilaudid, Exalgo) – 18mg, Oxymorphone (Opana, Opana ER) – 30mg).(All doses are the 24 hours dosage equivalent to 80mg morphine. Individuals at or above these daily doses should be considered opioid tolerant. If a patient is on a combination of 2 different medications, add the 2 equivalents together and see if it is equal to or above 80mg morphine. For example, if someone is on 30mg oxycodone daily (which is about 50mg morphine equivalents, given that 50mg oxycodone equals 80mg morphine) PLUS 50mg Hydrocodone (which is about equivalent to another 50mg morphine, given that 80mg hydrocodone equals 80mg morphine), then this person is a total of 100mg morphine equivalents daily).* 2) Patients taking opioid agonist or agonist/antagonists (e.g. suboxone, revia, vivitrol, contrive) If patient has a personal community pain physician or pain medication prescriber please provide contact info

Name _____ Telephone _____

TREATING ACUTE PAIN

- Uninterrupted treatment of opiate addiction and aggressive pain management for current situation
- Inadequate treatment of acute pain might lead to chronic pain
- Focus on multi modal analgesia

USE MULTIMODAL TREATMENT

- Multimodal Non-opioid Agents for Preemptive Analgesia
- Suggested Dose (Two hours before surgery)
  Acetaminophen PO 1000 mg (over 50 kg)
  Celecoxib PO 200-400 mg
  Pregabalin PO 75-150 mg
  Gabapentin PO 900-1200 mg

Consider Local Anesthesia when possible (Regional, Blocks, Infiltration)

Consider Infusion Ketamine and /or Lidocaine, Dexmedetomidate

MANAGEMENT OF PATIENTS TREATED WITH METHADONE

- For Patients Taking Other opioids- Convert
- Convert the calculated oral MED in IV dose of hydrochloride morphine, according to the oral:IV ratio for morphine of 3:1

Equianalgesic doses of opioids

Opioid	Approximate oral equianalgesic dose	Onset	Duration	Half-life
Morphine (reference drug)*	30 mg	2–3 h	8–12 h	2–4 h
Tramadol*	150 mg	1–2 h	8–12 h	2–4 h
Codeine (with APAP)	200 mg	30–60 min	4–8 h	3–4 h
Oxycodone*	20 mg	1–2 h	6–10 h	3–4 h
Hydromorphone	7.5 mg	12–14 h	20–24 h	8–16 h
Oxymorphone	10 mg	30–45 min	4–6 h	2–3 h
Hydrocodone (APAP, ASA, or ibuprofen)	30 mg	15–30 min	4–8h	2–3 h

TREATMENT- BUPRENORPHINE

- A derivative of Thebaine that is a more potent (25 - 40 times) analgesic than morphine. Partial agonist at mu and kappa antagonist
- Ceiling effect for both euphoria and respiratory depression
- About 30 times as potent as Morphine
- Extremely High receptor affinity. Highly lipophilic Highly protein binding
- Half life 37 hrs 5 half lives = approx. 7 days

Substance abuse and mental health services administration buprenorphine. 2018; HTTPS://www.SAMHSA.gov/medication-assisted-treatment/treatment/buprenorphine. July 6, 2018

TREATMENT- BUPRENORPHINE

- Treating Patients on this medication and Having Surgery
- What to do?
  Continue use?
  Decrease?
  Stop?
- How would/should I change my management of this patient?

TREATMENT OF ACUTE PAIN WITH CHRONIC ADDICTION

- Early and Close Communication with Team
- Conversion to morphine equivalents
- Methadone
  Take oral
  Change to SQ or IM
- Buprenorphine
  Continue-can be used for Acute Pain
  Hold for several Days

Principles of treating acute pain in a patient with opioid dependence.

Create a supportive, nonjudgmental environment
Establish whether other drugs are misused
Analgesic plan Optimize nonopioid analgesia Use increased doses of opioids compared with opioid-naive patients but with careful monitoring for side effects Change from parenteral to oral formulations of opioids as soon as possible
Withdrawal management plan Continue opioid substitution therapy or replace with an appropriate opioid Consider withdrawal syndromes of other drugs taken
Minimize stress
Allow for multidisciplinary discharge planning

RELAPSE

- Intravenous opiates- stronger reinforcing effect
- Oral opiates and sustained release opiates lower abuse potential
- Best treated with short acting formulations since acute pain fluctuates
- If patient currently abstinent- may not want to receive opiates or intravenous opiates for acute pain control- respect their wish
- Evidence demonstrates relapse is small with perioperative opiates evidence also demonstrates unrelieved pain can be a trigger as well for relapse

MEDICATIONS INEFFECTIVE

Quantitative sensory testing has shown that, similar to patients with pain taking long-term opioids, those abusing heroin and those on methadone and buprenorphine substitution therapy may develop hyperalgesia- Opioid-induced hyperalgesia

Opioid tolerance is the decreased effectiveness of opioids over time, such that higher doses are needed to achieve the same effect-Opioid tolerance

CDC STATEMENT

- **When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider**
- **urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs**

–

http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

URINE DRUG SCREEN

- Reasons
  - Is the patient taking the medication?
  - Is the patient taking any other medication written or otherwise?
  - Keeping patient honest
- Point of Care cup- immunoassay Med is there to react or not
  - Cheap
  - Easy
  - Immediate
- May have False positive and negative findings
  - Follow up with quantitative study
  - Cut off might be too high

URINE DRUG SCREEN

Low-Risk Level	UDT every 1-2 years	State drug monitoring program - 2x per year
Medium-Risk Level	UDT every 6-12 months	State drug monitoring program - 3x per year
High-Risk Level	UDT every 3 months	State drug monitoring program - 4x per year

From: Prescription of Controlled Substances: Benefits and Risks

URINE DRUG SCREEN

- Quantitative study
  - Lab
  - Expensive
  - Time
  -Tells you EXACTLY what is in the system

URINE DRUG SCREEN

- Use the simple and point of care-Baseline
- If Negative or Positive for any other substance- Send out for confirmation
- Point of care does NOT determine Quantity
- More expensive testing determines the EXACT amount
- Medication MUST be present
  - Prevent Diversion
  - Determines exact amount
  - Must change clinical course if Unusual finding

URINE DRUG SCREEN

- • Practice in America can vary with some not using UDT at all and others getting an excessive amount of UDT.
- **• The people performing an excessive amount of UDTs almost invariable are the owners or the one's who profit from the testing performed**. - Greed

URINE DRUG SCREENING

- • Confirm a person's relayed medical history
  - – Supports or refutes their use of licit and illicit chemicals
  - – Supports or refutes the medical regimen they are purported to be taking
- • Used to decide whether to initiate, continue or maintain a therapy

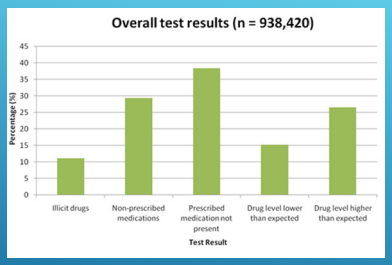
URINE DRUG SCREENING

- Random collection.
- Urinalysis must have a certain criteria
- temperature 90 to 100°F
- pH 4.5-8 .5
- creatinine greater than 20 mg/dl
- Before obtaining as patient what they are taking should we be looking for anything in this urine?
- If there any concerns or questions always send off to the lab for confirmatory testing.

URINE DRUG SCREEN

- Amphetamines / methamphetamines
- benzodiazepines
- barbiturates
- marijuana
- cocaine
- PCP
- methadone
- opioids (narcotics) Natural and synthetic

Urine detection of drugs (approximate duration in h/d).
Buprenorphine and metabolites: 8 d
Cocaine metabolite: 48–72 h
Methadone maintenance dosing: 7–8 d
Heroin (diamorphine), detected as morphine, codeine, dihydrocodeine, and propoxyphene: 48 h
Cannabinoids, single use: 3–4 d
Cannabinoids, heavy or chronic use: up to 45 d
Amphetamines: 48 h
Benzodiazepine (short acting, such as midazolam): 12 h
Benzodiazepine (long acting, such as diazepam): over 7 d



URINE DRUG SCREENING

URINE DRUG SCREENING WHO'S AT RISK?

People are evaluated for being low, moderate, or high risk for substance abuse

- – Low risk = 65% of populace = do not abuse now or in past chemicals or have psychiatric disease
- – Moderate risk = 15% of populace = people who will abuse/use chemicals both licit or illicit at times and people with psychiatric disease
- – High risk = 20% of populace = people who actively abuse or are addicted to chemicals (ie smokers)

URINE DRUG SCREENING WHO'S AT RISK?

- • Low risk patients
  - – Once a year or if there is an appearance of any aberrant disease
- • Moderate risk patients
  - – Once or more a year in addition to any appearance of any aberrant disease
- • High Risk patients
  - – With a frequency necessary to assure they are staying with the boundaries
  - • Some may require weekly testing

URINE DRUG SCREENING QUALITATIVE TESTING

- Tells you whether a chemical is present if it has a concentration in the UDT above a predetermined limit.
  - – If the test limit is 10 U/cc and you have 9 or less U/cc then the results would indicate that this chemical is not in your system
  - – If the test limit is 10 U/cc and you have 10 U/cc or above in your urine than the test would be positive.
  - – This testing does not give you any specific information about the exact concentration of a chemical in the urine. To know this number, you order a quantitative test.

URINE DRUG SCREENING QUANTITIVE TESTING AND FRAUD

- • He does quantitative testing in addition to qualitative testing for every patient which is substandard. Only qualitative testing with additional quantitative testing needs to be performed.
- • He tests every single patient getting opioids in his practice in the same manner every 2 months. This fraud in the guise of providing good medical care has netted him and/or the UDT company he directs in his office to **$5.8 million dollars/year** of overpayments by the government, patients and their insurance.
- • This fraud is known to have been occurring for years.

WHAT TO DO?

- Believe the patient.
- Let them know you're sending the qualitative urinalysis out for evaluation with specific testing.
- Let the patient know that the specific testing is never wrong.
- Let the patient have a chance to be honest if necessary.

FALSE POSITIVE RESULTS

- Antibiotics
- Antidepressants
- Antihistamines
- Antipsychotics
- Cold Remedies/Decongestants
- DHEA Hormone
- Ibuprofen
- Melanin
- OTC drugs
- Pain relievers
- Poppy seeds

https://www.confirmbiosciences.com/knowledge/terminology/drug-test-false-positive-false-negative/

SUMMARY

- History and Physical
- Documentation of Risk Factors
- Understand current Substance Use Disorder (treatment or remission?)
- Appreciate how much risk this patient is presenting(Do I attempt to treat?)
- Can the patient be treated in a non opiate format
- Will my treatment lead to relapse

SELF EVALUATION

Caring for Patients with Current or Past Substance Use Disorder

1. T/F - Patients with substance use disorder tend to have standalone issues from a psychiatric standpoint.

2. T/F - Usually one can assess patients for the risk of substance use disorder with a visual assessment and knowledge of the family background.

3. T/F - You have a patient on methadone at 80 mg a day. The patient is stable. Now, the patient presents with acute back pain in your office. Would it be reasonable to provide the patient with muscle relaxants and/or Medrol dose pack? Or given the fact that yhey are on methadone (a powerful pain medication) the medication should cover this patient's discomfort?

4. T/F - A patient is taking buprenorphine who is scheduled for an in office irrigation and drainage of a cyst. Continue this medication.

5. T/F - It is reasonable for patients with substance use disorder in active treatment for their medical issue to use co-analgesic medication such as multi modal therapy.

6. T/F - When patients are given more opiate therapy and their pain seems to be get worse this is known as hypoanalgesia.

7. T/F - If I have a patient in my practice who I am providing buprenorphine medication, I need to obtain a urine drug screen 4 times a year if they have been compliant with pill counts and office visits?

8. For patients obtaining a urine drug screen and there is a finding that was unintended, what are my next steps?

    a. Discharge the patient
    b. Continue to write medication and follow-up in another month
    c. Assume a lab error and continue to write for the medication
    d. Send the urine drug screen out for confirmation and discuss findings with patient

Answer Key: 1. F, 2. F, 3. F, 4. T, 5. T, 6. F, 7. F, 8. D

Joshua R. Meyerson, MD, MPH

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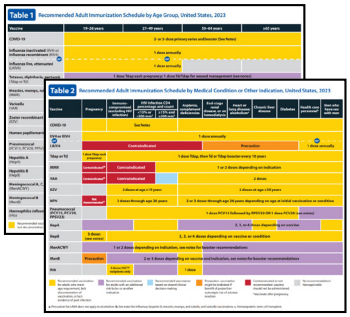
Routine, Risk-based and Travel Vaccines for Adults

2023 CDC Recommended Immunization Schedule For Adults



- Adult vaccination is based primarily on risk conditions
- Easy to use App
- Each February, CDC publishes updated adult immunization schedules

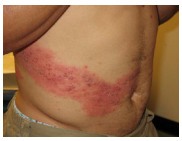
2023 (CDC) Adult Immunization Schedule

Strategies To Improve Immunization Practices

- Ensure patients **understand** recommended vaccines
  - Based on age, risk condition, occupation and/or lifestyle
- **Strongly** recommend vaccines
- **Assess** immunization status at every visit
- Offer **all recommended vaccines** at every visit
  - Be prepared to make referrals for vaccines not available
  - Follow true contraindications-do not miss opportunities
- **Document** administered vaccines in your State Registry
- **Remind** patients that family members and close contacts should also be fully vaccinated

Based on the "Standards for Adult Immunization Practice" and "Standards for Pediatric Immunization Practice"

Shingles



Courtesy of National Institute of Allergy and Infectious Diseases (NIAID)

- About 1 million cases of shingles in the US annually
- Lifetime risk of developing HZ is 1 in 3
- Your risk of getting shingles and having serious complications increases as you get older
- 10-18% develop PHN, increases with age
  - Persons younger than 40 rarely experience PHN
- May lead to serious complications of the eye including blindness

CDC About Shingles (Herpes Zoster)
Clinical Overview of Herpes Zoster (Shingles) | CDC

Herpes Zoster (HZ)

- RZV (Shingrix) is the vaccine for use in the prevention of herpes zoster
- Does not prevent infection, reduces risk of reactivation
- Inactivated Vaccine 2 doses 0, 2-6 months
- **Routine Recommendation:**
  - Recommended for immunocompetent adults 50 years and older, including:
    - Adults with prior receipt of varicella vaccine, zoster vaccine live (ZVL), or herpes zoster episode (once resolved)
- **Special Situations:**
  - Recommended for use in persons 19 years and older who are or who will be immunodeficient or immunosuppressed because of disease or therapy

ACIP Zoster Vaccine Recommendations | Shingles | CDC

Hepatitis A Vaccine

- Recommended for all children beginning at age 12 months
- Recommended for adults who are at high-risk for disease-including outbreaks
- Recommended for Travel to endemic areas (most developing countries)
- Spreads person to person or contaminated Food and Water
- Can be offered to anyone who wants protection
- 2 doses 6 months apart lifetime protection (no boosters)

Risk factors include chronic liver dz including Hep B or C, HIV, MSM, SUD, close contacts of cases

Hepatitis B (HepB) Vaccine

- Recommendations for HepB **routine vaccination** include:
  - All children routinely recommended
  - **Catch-up all unvaccinated persons through age 59 years**
- High Risk Adults:
  - Occupational risk, Hemodialysis patients
  - All STD clinic clients, Multiple sex partners, Prison inmates
  - MSM, HIV, IDU
- Dosing Schedule is dependent on age, vaccine, and condition – usual 3 dose or newer 2 dose vaccine
  - Shorter or longer dosing schedules may be recommended
  - For more details, please refer to the Schedules

Influenza Vaccine: Everyone, Every Year

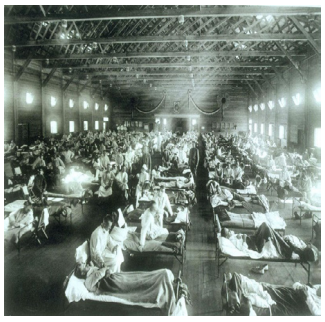


Photo Courtesy of the National Museum of Health and Medicine

- Recommended for all person's aged 6 months and older
- Continue to ensure that persons at higher risk for influenza related complications, and those around them, are vaccinated
- All are quadrivalent

Influenza Vaccination for Persons 65 Years and Older

ACIP now recommends that adults aged 65 years and older preferentially receive any one of the following higher dose or adjuvanted influenza vaccines:

- Quadrivalent high-dose inactivated influenza vaccine (HD-IIV4),
- Quadrivalent recombinant influenza vaccine (RIV4), or
- Quadrivalent adjuvanted inactivated influenza vaccine (aIIV4)

If none of these three vaccines are available at an opportunity for vaccine administration, then any other age-appropriate influenza vaccine should be administered

COVID-19 Vaccine Clinical Considerations

- Recommendations changed rapidly as the pandemic evolved, now endemic infection with lower overall but continued risk
- Bivalent mRNA vaccine

COVID-19 Vaccination Clinical Resources

Coadministration

- COVID-19 vaccines **may be administered without regard to timing of other vaccines**
- This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day
- If multiple vaccines are administered at a single visit, administer each injection in a different injection site
- Best practices for multiple injections include:
  - Separate injection sites by 1 inch or more, if possible
  - Administer the COVID-19 vaccine and vaccines that may be more likely to cause a local reaction in different limbs, if possible

Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC

Pneumococcal Vaccines

- There are 2 types of Pneumococcal Vaccines in the U.S.:
  - Pneumococcal Conjugate Vaccines (PCV13, PCV15, PCV20)
  - PCV15 and PCV20 replacing PCV13 for adult use
  - Pneumococcal Polysaccharide (PPSV23)
- Recommendations are based on age and medical condition
- Reduces risk of Pneumococcal Pneumonia and Invasive Pneumococcal Disease – Meningitis, Sepsis

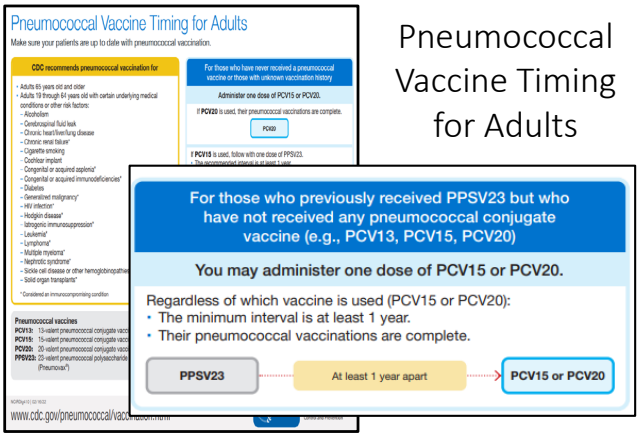
Table 1
Recommendations for adults who have never received a pneumococcal conjugate vaccine, by underlying medical condition or other risk factor and age group

Underlying medical condition or other risk factor	19 through 64 years old	≥ 65 years old
None	Not recommended	Administer 1 dose of PCV20 OR 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later
Alcoholism Chronic heart disease† Chronic liver disease Chronic lung disease‡ Cigarette smoking Diabetes mellitus Cochlear implant Cerebrospinal fluid leak Chronic renal failure* Congenital or acquired asplenia* Congenital or acquired immunodeficiency*¶ Generalized malignancy* HIV infection* Hodgkin disease* Iatrogenic immunosuppression*¶ Leukemia* Lymphoma* Multiple myeloma* Nephrotic syndrome* Sickle cell disease/other hemoglobinopathies* Solid organ transplant*	Administer 1 dose of PCV20 OR 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later *The minimum interval (8 weeks) can be considered in adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.*	Administer 1 dose of PCV20 OR 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later *The minimum interval (8 weeks) can be considered in adults with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.* *Reminder: No additional doses are indicated at this age if PCV15 or PCV20 were administered at a younger age.*

* Considered an immunocompromising condition
† Includes congestive heart failure and cardiomyopathies
‡ Includes chronic obstructive pulmonary disease, emphysema, and asthma
¶ Includes B- (humoral) or T-lymphocyte deficiency, complement deficiencies (particularly C1, C2, C3, and C4 deficiencies), and phagocytic disorders (excluding chronic granulomatous disease)
§ Includes diseases requiring treatment with immunosuppressive drugs, including long-term systemic corticosteroids and radiation therapy

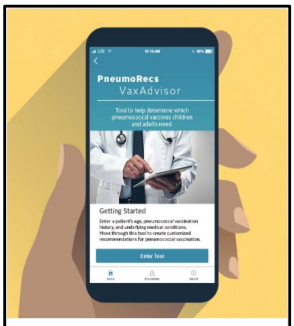
Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine

Pneumococcal Vaccine Timing for Adults



Pneumococcal Vaccine Timing for Adults-February 16, 2022 (cdc.gov)

Pneumo Recs VaxAdvisor Mobile App for Providers



PneumoRecs VaxAdvisor is available for download on iOS and Android mobile devices.

Quickly and easily determine which pneumococcal vaccines a patient needs and when

Incorporates recommendations for all ages so internists, family physicians, pediatricians, and pharmacists alike will find the tool beneficial

Desktop Version also available

PneumoRecs VaxAdvisor: Vaccine Provider App | CDC

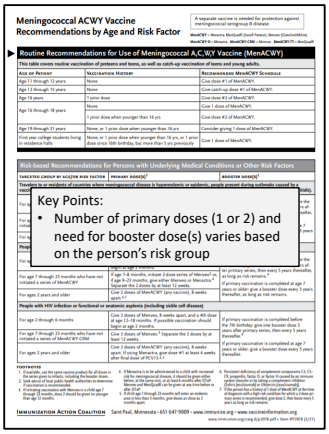
Meningococcal Disease Burden

- Serogroup B and C are the major causes of meningococcal disease in the U.S.
  - Each responsible for approximately 25-40% of cases
- Proportion of U.S. serogroup disease varies by age group
  - B: 60% of disease among children and young adults under 24 years of age
    - College students have more than 3X the risk of serogroup B as similarly aged people not attending college
  - C, Y, W-135: 60% of all cases of meningococcal disease among persons 24 years of age and older
- Overall case fatality of meningococcal disease is 10-15% even with appropriate antimicrobial therapy
  - Can be even higher in persons with meningococcemia
- Approximately 20% of survivors have permanent sequelae such as: hearing loss, neurological damage, or loss of limb

Epidemiology and Prevention of Vaccine Preventable Diseases, 14th Edition, 2021

Persons at Increased Risk for Meningococcal ACWY Disease

- Adolescents
  - Including college freshmen living in dorms
- **Persons with certain medical conditions**
  - **Asplenia (functional or anatomic)**
  - **Persistent terminal complement component deficiency**
  - **HIV**
  - **Anyone taking a complement inhibitor such as Soliris® or Ultomiris®**
- Persons who are living in or traveling to:
  - Areas with a high incidence of disease (i.e., parts of Africa)
  - Mecca during the annual Hajj (required for entry)
- Occupational risk
  - Microbiologists exposed to *N. Meningitides*
  - Military recruits
- Persons exposed to disease during a current community outbreak



Meningococcal B Vaccine Recommendations

- Administer to persons aged 10 years and older
  - With persistent terminal complement component deficiency
  - With asplenia (anatomic or functional)
  - Who are taking a complement inhibitor such as Soliris® or Ultomiris®
  - Who are exposed during a community outbreak
  - Who are microbiologists exposed to *N. Meningitides*
- Based on shared clinical decision making, persons aged 16-23 not in a high-risk group, may be vaccinated
  - Providers need to discuss risks and benefits with these persons
  - Series preferably given at ages 16-18 years

Meningococcal Vaccination for Adolescents: Information for Healthcare Professionals

Meningococcal B (MenB)

- Meningococcal B Vaccines
  - Bexsero (Novartis) 2 doses at least 4 weeks apart
  - Trumenba (Pfizer) 2 doses at 0, 6 months **or** 3 doses at 0, 2, 6 months[1]
- Same brand must be used to complete the series
- MenACWY and MenB vaccines may be given at same visit

[1]Young adults aged 16 through 23 years who are healthy and not at increased risk for MenB disease may receive a 2-dose series of Trumenba at 0 & 6 months for short term protection against most strains of MenB disease. **All other persons are recommended to receive a 3-dose series, including those in an outbreak.** This is found in the notes of the 2023 Children and Adolescent Immunization Schedule

MenB Booster Recommendations

- Persons aged 10 years and older with:
  - Complement deficiency, complement inhibitor use, asplenia, who are microbiologists
    - Give a MenB booster dose 1 year following completion of a MenB primary series
    - Followed by MenB booster doses every 2-3 years thereafter, for as long as increased risk remains

HPV Infection

- By age 50, at least 4 out of every 5 (at least 80%) women will have been infected with HPV at one point in their lives. HPV is also very common in men[1]
  - More than 42 million Americans are currently infected with HPV types that cause disease
  - About 13 million Americans become infected each year
  - HPV infection is most common in people in their late teens and early 20s
- Easily spread by intimate skin-to-skin contact during sexual activity
  - Not just with sexual intercourse
- Most people will never know they have been infected

[1]Basic Information about HPV and Cancer
CDC Basic Genital HPV Infection-Fact Sheet
HPV Infection | Human Papillomavirus (HPV) | CDC

HPV-Attributable Cancers

- Annually in the U.S., an average of 46,143 new cases of cancer occur in parts of the body where mucosal HPV types are found*
  - Cervix, vagina, vulva
  - Anus, penis
  - Oropharynx (more common in men)
- Of these, about 33,700 attributed to HPV types that are preventable with the 9-valent HPV vaccine

* Based on Data from 2014 to 2018

HPV-Associated Cancer Statistics
United States Cancer Statistics Data Brief No.26 December 2021
CIDRAP-Study Finds High Burden of Oral HPV Related Cancers in Men

HPV Vaccine Points

9vHPV Serotypes:	6, 11, 16, 18, 31, 33, 45, 52, 58
Protection Against:	Cervical, vaginal, vulvar, penile, anal, oropharyngeal cancers; genital warts; precancerous or dysplastic lesions
Licensed for Ages:	9 through 45 years
Routine Age:	Age 11-12 years
Catch-Up Age:	Males and Females through 26 years of age
Adults 27-45:	Shared clinical decision-making[1]

[1]HPV vaccine may benefit some adults aged 27 through 45 years who are not adequately vaccinated. Providers, through shared clinical decision, can discuss HPV vaccination with persons who are most likely to benefit.

HPV Vaccine Recommendations

- For persons who initiate HPV series at/after age 15 years and for persons who are immunocompromised (regardless of age at 1st dose), use **a 3-dose schedule** (0, 1-2, 6 months)
  - Minimum intervals: Dose 1 to 2 = 4 weeks; Dose 2 to 3 = 12 weeks; Dose 1 to 3 = 5 months
- Persons with a complete HPV series are not recommended to receive any additional doses
- While not contraindicated, HPV is not recommended during pregnancy
- Must be given IM (SC dose should be repeated)

Tetanus, diphtheria and pertussis (Tdap)

- Given routinely at age 11-12 years
- Vaccinate all persons aged 13 years & older without a previous documented dose of Tdap
  - To ensure continued protection against tetanus and diphtheria, booster doses of either Td or Tdap should be administered every 10 years throughout life
- 2019 National adult immunization rates[1]
  - Age 18 years and older: 43.6%
- To ensure pertussis protection, Tdap can be administered regardless of interval since last tetanus or diphtheria-toxoid containing vaccine

[1]AdultVaxView | General Population Reports | Vaccination Coverage | CDC

Strategies for Protecting Infants

- Vaccination during pregnancy
  - **Should receive 1 dose of Tdap during every pregnancy**
    - Preferably during the **early part** of 3rd Trimester
    - Will best ensure maternal antibody transfer to the fetus
  - If Tdap was **not** administered anytime **prior to or during** pregnancy, give Tdap immediately postpartum (not optimal)
- Study reported that vaccination with Tdap during the 3rd trimester prevented more than 3 out of 4 cases of whooping cough in babies less than 2 mos. old
- "Cocoon" the infant
  - All adults and adolescents at least 11 years old who have not previously received a Tdap vaccination, should be vaccinated at least 2 weeks before coming into close contact with a newborn (i.e., father, siblings, grandparents, caregivers)

New Study Shows Tdap Vaccination During Pregnancy can Prevent Whooping Cough in Babies

Tetanus Prophylaxis Guidelines

Routine: 1 Dose Td or Tdap every 10 years

Previously did not receive primary series: 1 dose Tdap followed by Td or Tdap in 4 weeks and 3rd dose 6-12 months

Wound Management:

- Clean and Minor wounds administer Td or Tdap if over 10 years since last dose
- All other wounds administer Td or Tdap if > 5 years

Monkeypox Virus (MPV)

- Mpox can spread to anyone through close, personal, often skin-to-skin contact; symptoms include a rash and fever
- Caused by a virus in the same family as the virus that causes smallpox
  - Typically results in milder infection
- Many of those affected in the 2022 outbreak are men who have sex with men (MSM). However, anyone who has been in close contact with someone who has MPV can get the illness
- Most infections last 2-4 weeks and resolve without specific treatment

About Monkeypox | Monkeypox | Poxvirus | CDC

JYNNEOS Vaccine

- Made available through the SNS to LHD and other agencies
- There is no cost to the individual for the vaccine
- Can be used as PEP and PrEP for those at increased risk

https://www.cdc.gov/poxvirus/mpox/vaccines/index.html

- Given 0.5ml SC or 0.1ml ID 2 Doses 4 weeks apart

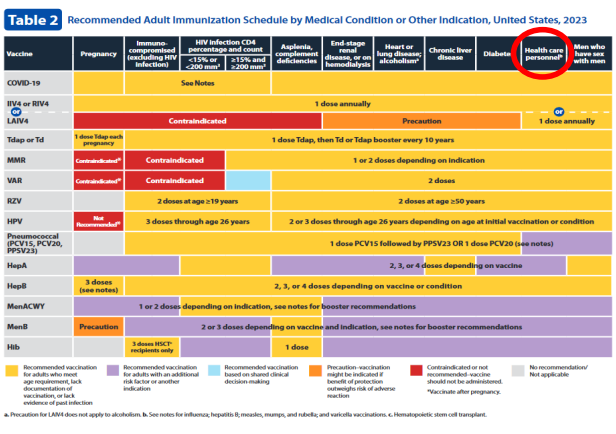


Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2023

Vaccine	Pregnancy	Immuno-compromised (excluding HIV infection)	HIV infection CD4 percentage and count <15% or <200 mm³	HIV infection CD4 percentage and count ≥15% and ≥200 mm³	Asplenia, complement deficiencies	End-stage renal disease, or on hemodialysis	Heart or lung disease, alcoholism[a]	Chronic liver disease	Diabetes	Health care personnel[b]	Men who have sex with men
COVID-19		See Notes									
IIV4 or RIV4	1 dose annually										
LAIV4	Contraindicated					Precaution				1 dose annually	
Tdap or Td	1 dose Tdap each pregnancy	1 dose Tdap, then Td or Tdap booster every 10 years									
MMR	Contraindicated[c]	Contraindicated	1 or 2 doses depending on indication								
VAR	Contraindicated[c]	Contraindicated		2 doses							
RZV	2 doses at age ≥19 years				2 doses at age ≥50 years						
HPV	Not Recommended[d]	3 doses through age 26 years			2 or 3 doses through age 26 years depending on age at initial vaccination or condition						
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)										
HepA	2, 3, or 4 doses depending on vaccine										
HepB	3 doses (see notes)	2, 3, or 4 doses depending on vaccine or condition									
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations										
MenB	Precaution	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations									
Hib	3 doses HSCT recipients only			1 dose							

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection. Recommended vaccination for adults with an additional risk factor or another indication. Recommended vaccination based on shared clinical decision-making. Precaution: vaccination might be indicated if benefit of protection outweighs risk of adverse reaction. Contraindicated or not recommended: vaccine should not be administered. *Vaccinate after pregnancy. No recommendation/ Not applicable

a. Precaution for LAIV4 does not apply to alcoholism. b. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. c. Hematopoietic stem cell transplant.

Health Care Personnel

- Assure Immunity to MMR, Varicella
  - 2 doses of vaccine OR Evidence of Immunity
- Antibody to Hepatitis B Surface Antigen
- Tdap
- Influenza – every year
- Covid-19 – Up to date

Both for protection of the employee as well as patient safety

Polio?

- It had been eradicated from Western Hemisphere for many years – Rockland County New York with circulating virus July 2022
- One-time single booster dose for adults if travelling to an area with endemic polio
- No current recommendations for adults unless in an area with active outbreak within the US
- Most adults in US have received polio vaccine
- See CDC Travel recommendations https://wwwnc.cdc.gov/travel
- Wild Polio still endemic in Nigeria, Pakistan, Afghanistan

Traveler Immunizations

- **Required?**
  - Yellow Fever
  - Meningococcal
    - Men ACWY only
- **Recommended?**
  - Polio
  - Tdap
  - Influenza & Covid-19
  - Measles
  - **Hepatitis A**
  - Typhoid
  - Cholera
  - Rabies
  - Japanese Encephalitis

Just as Important

- Most travel related illness not preventable with vaccines
- Safe Food – cook it, peel it, wash it, or forget it
- Safe Water – filters, UV Purifier (steripens), tablets, bottled
- Preventing Mosquito Bites (malaria, dengue, etc.) – DEET, clothing, bed nets
- Malaria Prophylaxis - consider for longer periods of travel based on specific location within country, meds dependent on resistance patterns
- CDC Travel website excellent resource – www.cdc.gov/travel
- Have a good first aid kit, basic meds and antibiotics such as Azithromycin, Cipro

Meningococcal Disease

- "Meningitis Belt"
  - Sub-Saharan Africa
- Greatest risk: dry season (Dec. - June)
- Risk of travelers
  - 0.4/100,000
- Hajj pilgrimage to Saudi Arabia associated with outbreaks
- Boosters if > 5 years since last Men ACWY

Typhoid Fever

- Typhoid fever – acute life-threatening illness
- Caused by *Salmonella typhi*
- Humans – only source
- Acquired through fecal contamination of food and water
- 22,000,000 cases worldwide/year
- SE Asia 6-30 times more common
- Smaller but still increased risk in other Africa, S. America, Caribbean
- Risk increases with time spent

Typhoid Vaccines

Vivotif®
- Oral, live-attenuated
- Ages 6 and older
- 50-80% protection
- 4 pills – one every other day
- Completed 1 week before potential exposure
- Revaccination every 5 years
- Can be prescribed and filled at local Rx

Typhim Vi®
- Capsular polysaccharide (IM)
- Ages 2 and older
- 50-80% protection
- Single 0.5ml injection
- 2 weeks before exposure
- Booster every 2 years

Yellow Fever

- Mosquito-borne viral hemorrhagic fever - *Flavivirus*
- ~200,000 cases per year, most in Africa
- Case fatality rates vary 20-50%, but Rare in travelers since vaccine introduction
- Incubation 3-6 days
- Fever, malaise, jaundice can lead to hepatic, renal failure, hemorrhage

Yellow Fever Vaccine

- Live-attenuated vaccine
- Developed in 1936
- Seroconversion >95%
- Single dose 0.5ml subcutaneously for persons over 9 mos of age who are at increased risk of disease or are required for entry.
- Revaccination at 10-year intervals no longer recommended by World Health Organization
  - One dose provides lifelong protection for most people
  - Some countries may still require booster within 10 years, or a booster may be recommended if travelling to an area with active outbreak.

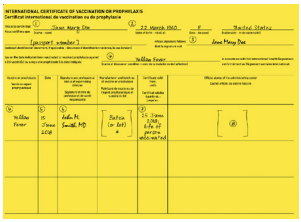
Yellow Fever Vaccine-Contraindications

- Age <9 months old
  Can consider at 6-9 months old during outbreaks
- Pregnant women
- Severe egg allergies or allergy to vaccine component
- Severe immunocompromise
- Immunomodulatory drugs
- Not a CI but should not donate blood for 14 days after vaccination.

Yellow Fever Vaccine

- Vaccine given at a certified center only
- https://wwwnc.cdc.gov/travel/yellow-fever-vaccination-clinics/search

International Certificate of Vaccination or Prophylaxis against Yellow Fever form (ICVP) or "yellow card" with physician signature, Uniform Stamp



Yellow Fever Vaccination Required for Entry

- Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Rep., Cote d'Ivoire, DR Congo, Equatorial Guinea, French Guiana, Gabon, Ghana, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Republic of Congo, Sierra Leone, South Sudan, Togo

Many more require proof of vaccination if arriving from a region with Yellow Fever

Always check an up-to-date list at www.cdc.gov/travel

Cholera

- *Vibrio cholera* from contaminated food/water
- New Vaccine for use in USA ***Vaxchora***
- Live Attenuated Oral single dose 10 days before travel lasts 3-6 mos
- Only if travelling to area with active transmission – endemic or outbreak
- Areas in Africa, SE Asia, Haiti currently (Jan 2023) with identified outbreak

Japanese Encephalitis Virus (JEV)

- Most common cause of encephalitis in Southeast Asia
- Carried by mosquitoes
- Risk
  - Little risk in urban areas
  - Recent outbreak in Australia

Consider JE Vaccine if

> one month in rural areas in endemic region

2 doses 28 days apart

Geographic distribution in Southeast Asia.

Map from www.cdc.gov

SELF EVALUATION

Routine, Risk-based and Travel Vaccines for Adults

1. Best practices for health professionals who administer vaccines include which of the following?

a. Assess immunizations status at every visit
b. Strongly recommend vaccines at every visit
c. Follow true contraindications for vaccines and avoid missed opportunities
d. Provide education on benefits of vaccination
e. All of the above

2. T/F - Shingles Vaccine can be given to anyone 50 years of age and older who has not received Recombinant Zoster Vaccine (RZV) previously.

3. T/F - Persons with chronic Hepatitis C infection should receive all recommended doses of Hepatitis A and Hepatitis B Vaccine.

4. Preferred Influenza Vaccination in those 65 years of age and older include which of the following:

a. Quadrivalent high-dose inactivated influenza vaccine (HD-IIV4)
b. Quadrivalent recombinant influenza vaccine (RIV4)
c. Quadrivalent adjuvanted inactivated influenza vaccine (aIIV4)
d. All of the above

5. Which of the following is NOT an indication for vaccination with Meningococcal B Vaccine?

a. Functional or anatomic asplenia
b. Taking a complement inhibitor medication such as Soliris or Ultomiris
c. Someone with planed travel to the “meningitis belt” of Africa
d. Someone exposed during a community outbreak of Meningococcal B disease

6. Which of the following is not recommended specifically for health care workers?

a. Hepatitis B Vaccine with evidence of immunity to Hepatitis B surface antigen
b. 2 Doses of Measles/Mumps/Rubella Vaccine or proof of immunity
c. 2 Doses of Hepatitis A Vaccine
d. 2 doses of Varicella Vaccine or proof of immunity
e. Seasonal Influenza Vaccine

7. T/F - All Adults without proof of polio vaccination should receive a booster dose.

Answer Key: 1. E, 2. T, 3. T, 4. D, 5. C, 6. C, 7. F

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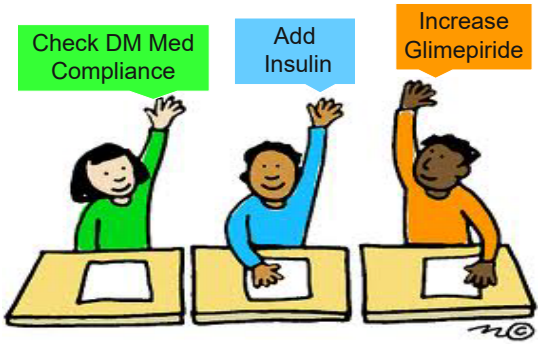
New Directions in Type 2 Diabetes

An Abbreviated Case Study

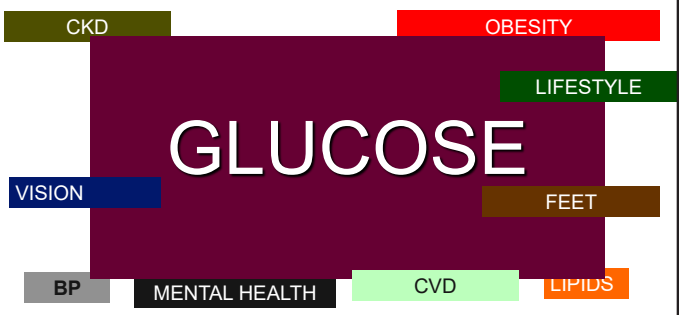
64 y.o. aSx Obese ♀(BMI 33.5), T2DM X 15 yrs
- PMH: MI 2 years ago
  - Metformin 1g b.i.d. + Glimepiride 4mg qd
  - ASA 81 mg qd
  - Atorvastatin 40 mg qd
- Glucose
  - FBS: 160-200 mg/dL
  - Lunch postprandial: 220-300 mg/dL
- HbA1c = 9.8

WHAT SHOULD WE DO NEXT?

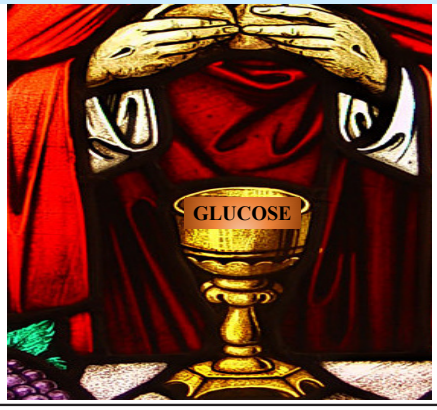
WHAT SHOULD WE DO NEXT?



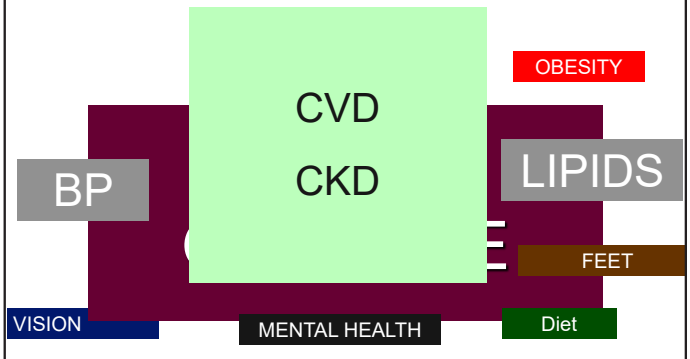
WHAT' s THE PROBLEM?



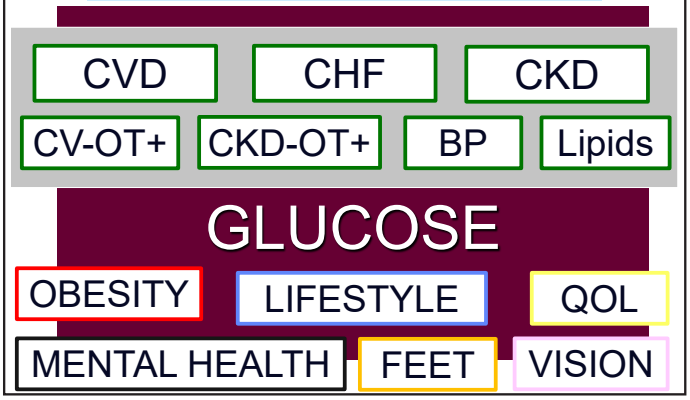
The "Holy Grail' of Diabetes



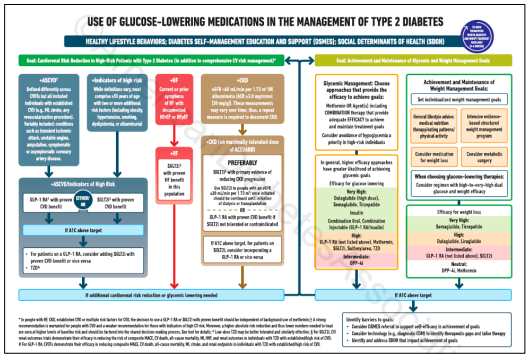
What's THE Problem?



DM: Problem Re-Stratification

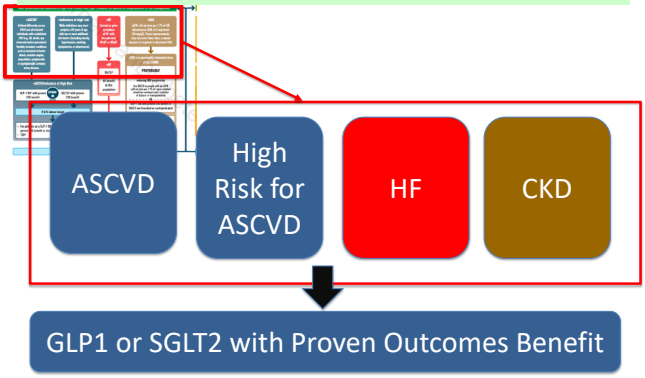


ADA 2023 Pharmacologic Rx Pathway



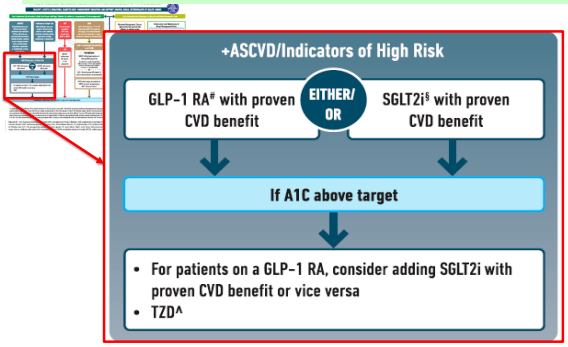
Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

ADA 2023 Pharmacologic Rx Pathway



Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

ADA 2023 Pharmacologic Rx Pathway



Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

The "Holy Grail' of Diabetes

DM and CVD Risk
A New Concept?

Why CVD? Mortality in DM

CAUSE	% of DEATHS
• Ischemic Heart Disease	40%
• Other Heart Disease	15%
• Acute Diabetic Complication	13%
• Cancer	13%
• Stroke	10%
• Pneumonia & Influenza	4%
• All others	5%

Geiss LS, et al. *Diabetes in America* 2nd ed. 1995:233-257

Why CVD Reduction?

"ASCVD — defined as CHD, cerebrovascular disease, or PAD presumed to be of atherosclerotic origin — is the leading cause of morbidity and mortality for individuals with diabetes…."

ADA Standards of Medical Care in Diabetes 2021
Diabetes Care 2021;44(Suppl 1):S125-S150

Mortal Consequences of Diabetes: Why?

" DM not only doubles or quadruples CV risk, compared with the general population, but also leads to an increased risk of cancer…."

Boena-Diez J et al *Diabetes Care* 2016;39:1987-1995

Mortal Consequences of Diabetes

"The average life expectancy of a 50-year-old individual with DM is 6 years shorter than it would be without the disease."

Boena-Diez J et al *Diabetes Care* 2016;39:1987-1995

DM and Women: CV Mortality
Nurses Health Study 1976-1996

Baseline Status **n = 121,700 RNs age 30-55**	**CV Mortality RR**
Control	1
DM no CHD	4.86
CHD no DM	7.46
CHD & DM	20.1

Hu FB et al *Arch Intern Med* 2001;161:1717-1723

Diabetes & Heart Failure

"Recent studies have found that rates of incident heart failure hospitalization….were twofold higher in patients with diabetes compared with those without. "

ADA Standards of Medical Care in Diabetes 2021
Diabetes Care 2021;44(Suppl 1):S125-S150

GLUCOTROL XL®
(glipizide)
Extended Release Tablets
For Oral Use

Prescribing Information

Glucotrol XL Prescribing Information (2016) (glipizide)

PRECAUTIONS

General

Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUCOTROL or any other anti-diabetic drug

Glucotrol XL Prescribing Information (2016) (glipizide)

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CV MORTALITY:

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

(Emphasis added)

Glucotrol XL Prescribing Information (2016) (glipizide)

WARNINGS

SPECIAL WARNING ON INCREASED RISK OF CV MORTALITY:

This warning is based on the study conducted by the UGDP, a long-term PCT trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes.

UGDP (University Group Diabetes Program)

- Study: T2DM (n=823)
- Rx (X9 years): Diet +
  - Fixed dose insulin (weight based12-16 u/d)
  - Variable dose insulin (to normalize glucose)
  - SFU (Tolbutamide)
  - Placebo
- Outcome: Cardiovascular Events

Meinert CL "The Trials & Tribulations of the UGDP" 2015 Kelmscott Bookshop, Baltimore

UGDP (University Group Diabetes Program)

Diabetes 1970;19:(Suppl 2):747-830

Results: CV mortality

- SFU (Tolbutamide) vs placebo RR = 2.5*
- Insulin vs placebo RR = ±1**

*Glucotrol PI.

**Meinert CL "The Trials and Tribulations of the UGDP" 2015 Kelmscott Bookshop, Baltimore

2014

Original Investigation

Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus

The AleCardio Randomized Clinical Trial

A. Michael Lincoff, MD; Jean-Claude Tardif, MD; Gregory G. Schwartz, MD, PhD; Stephen J. Nicholls, MBBS, PhD; Lars Rydén, MD; Bruce Neal, PhD; Klas Malmberg, MD; Hans Wedel, PhD; John B. Buse, MD, PhD; Robert R. Henry, MD; Arlette Weichert, MD; Ruth Carmeta, RN; Anders Svensson, MD; Dietmar Volz, PhD; Diederik E. Grobbee, MD, PhD; for the AleCardio Investigators

IMPORTANCE No therapy directed against diabetes has been shown to unequivocally reduce the excess risk of cardiovascular complications. Aleglitazar is a dual agonist of peroxisome proliferator-activated receptors with insulin-sensitizing and glucose-lowering actions and favorable effects on lipid profiles.

Lincoff AM et al *JAMA* 2014;311(15):1515-1525

BP Targets
ADA Standards of Care 2023

"The on-Rx target BP goal is <130/80 mmHg, if it can be safely attained." (**B**)

Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

ADA 2023 HTN Rx
Goal BP 130/90 (if baseline <160/100)

Monotherapy

ALBUMIN or CAD
ACE/ARB

OTHERS
ACE/ARB
CCB*
Diuretic**

* dihydropyridine
** chlorthalidone or indapamide

Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

HTN Pharmacologic Rx:
Initial BP > 160/100 mmHg

Start 2 Agents

Albuminuria or CAD

NO → Any 2: ACE/ARB, CCB*, Diuretic*

YES → ACE/ARB + CCB* or Diuretic*

* chlorthalidone or indapamide preferred

Diabetes Care 2022;45(Suppl 1):S144-174

ADA 2023 Lipid Recommendations

Age	CAD	Statin Intensity	LDL Goal	Evidence
40-75	NONE	Moderate	NS*	A
40-75	High Risk	High	<70 mg/dL	B
All	ASCVD	High	<55 mg/dL	B
20-39	RF+	Yes	NS*	C

Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

Antiplatelet Rx

Category	Agent	Evidence Level
2^0 Prevention	ASA 75-162 mg/d Clopidogrel if ASA Allergy	A
1^0 Prevention	*ASA 75-162 mg/d	A

*After risk/benefit discussion

Diabetes Care 2022;45(Suppl 1):S144-174

ADA 2023 Recommended A1C/CGM Goals
"Many Non-Pregnant Adults"

A1c:
<7% (Absent Hypoglycemia)
(Evidence A)

CGM:
TIR >70% and TBR <4% (Time <54 mg/dL <1%)
(Evidence B)

Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

ADA 2023 Recommended A1C/CGM Goals When A1c < 7% Might Be Appropriate

"On the basis of provider judgment and patient preference…lower A1c levels than the goal of 7% may be acceptable, and even beneficial, if it can be achieved safely without significant hypoglycemia or other adverse effects of Rx" (**C**)

Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

ADA 2023 Recommended A1C Goals When A1c < 8% Might Be Appropriate

- Limited life expectancy
- Rx harms > benefits (B)

Elsayed NA, et al *Diabetes Care* 2023;46(Suppl.1):S140-S157

Pharmacotherapy 1st Things 1st

"…GLP1RA, SGLT2i, **with or without metformin** based on glycemic needs **are appropriate initial Rx** for …T2DM with high risk for ASCVD, HF, and/or CKD." **A**

Diabetes Care 2022;45(Suppl. 1):S125–S143

T2DM Pharmacotherapy 1st Things 1st: ASCVD

"…[with] established ASCVD or indicators of high CVD risk,…CKD, or HF, an SGLT2i and/or GLP1-RA with demonstrated CVD benefit is recommended…**independent of A1c**…." **A**

High Risk = 10 yr CVD risk ≥ 15%

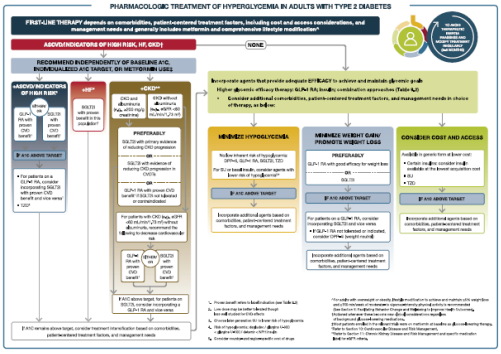
Diabetes Care 2022;45(Suppl. 1):S125–S143

T2DM Pharmacotherapy Metformin & CVD: Maybe

"Metformin is effective and safe, is inexpensive and **may** reduce risk of CV events and death."

Diabetes Care 2022;45(Suppl. 1):S125–S143

ADA T2DM Pharmacotherapy Map



Diabetes Care 2022;45(Suppl. 1):S125–S143

Pharmacotherapy Decision Point #1
Is My Patient in a Dominant Risk Category?

ASCVD, High Risk for ASCVD, HF, CKD

⬇

Recommended Rx is INDEPENDENT of A1c, A1c Target, or Metformin

⬇

Same Choices Activated Upon INCIDENT ASCVD (or High Risk), HF, CKD

Diabetes Care 2022;45(Suppl. 1):S125–S143

Pharmacotherapy Decision Point #2
Rx as Per Dominant Risk Category: ASCVD

ASCVD, High Risk for ASCVD

⬇

Step 1: GLP1R-RA* or SGLT2i *

A1c Not at Goal ⬇

Step 2: Add SGLT2i to GLP1-RA and vice versa

A1c Not at Goal ⬇

Step 3: Add TZD

* **Choose agent with proven benefit**

Diabetes Care 2022;45(Suppl. 1):S125–S143

Pharmacotherapy Decision Point #2
Rx as Per Dominant Risk Category: HF

Heart Failure

⬇

Step 1: SGLT2i *

A1c Not at Goal ⬇

Step 2: Individualized

* **Choose agent with proven benefit**

Diabetes Care 2022;45(Suppl. 1):S125–S143

Pharmacotherapy Decision Point #2
Rx as Per Dominant Risk Category: CKD

CKD

⬇

Step 1: SGLT2i * [or GLP1-RA if no albuminuria]

Not tolerated ⬇

Step 2: GLP1-RA for CV risk reduction *

A1c Not at Goal ⬇

Step 3: Add SGLT2i to GLP1-RA and vice versa

* **Choose agent with proven benefit**

Diabetes Care 2022;45(Suppl. 1):S125–S143

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

FDA 2008 Guidance for Industry

"Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat T2DM is not associated with an **unacceptable increase** in CV risk."

Emphasis added

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf accessed January 6, 2019

How Does Industry Respond to the FDA 2008 Guidance for Industry?

Performing Non-inferiority Trials

- New Drug A vs Placebo added to existing Rx

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf accessed January 6, 2019

What Does a Non-Inferiority Trial Demonstrate?

"New Drug A has been found to be 'non-inferior' to Old Drug B" means:

- Drugs A and B are equally effective NO
- New Drug A is not more than a pre-specified amount **less** effective than Old Drug B YES
- New Drug A (given, usually, similar efficacy), is not more than a pre-specified amount **more toxic** than Old Drug B YES

What Does "Non-Inferiority" Mean In Terms of CV Outcomes for New T2DM Drugs?

- New Drug A incurs <30% increase in CV risk

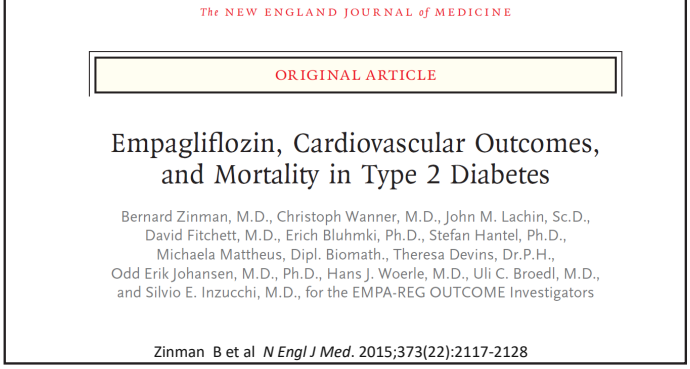
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf accessed January 6, 2019

CV Safety Trial Showing CV Risk REDUCTION Canagliflozin

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio* (95% CI)
	Cana	Pbo	
CV death, nonfatal MI & stroke[a]	2.69	3.15	0.86 (0.75-0.97)
HF hospitalization	0.55	0.87	0.67 (0.52-0.87)
CV death or HF hospitalization	1.63	2.08	0.78 (0.67-0.91)
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)
40% ↓ eGFR, renal dialysis or transplantation, renal death	0.55	0.90	0.60 (0.47-0.77)

Neal B, et al. *N Engl J Med*. 2017;doi:10.1056/NEJMoa1611925.

CV Safety Trial Showing CV Risk REDUCTION Empagliflozin


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

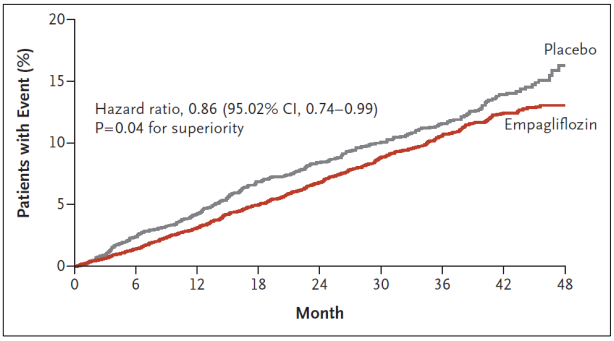
Zinman B et al *N Engl J Med*. 2015;373(22):2117-2128

CVOT: Empagliflozin (EMPA-REG)

- Study: RDBPCT T2DM Adults (n=7,020)
- Rx: empagliflozin 10 or 25 mg qd
- Inclusion :
  - ASCVD +
  - GFR >30
  - BMI <45
- 1^0 Outcome: CV death, nonfatal MI & stroke

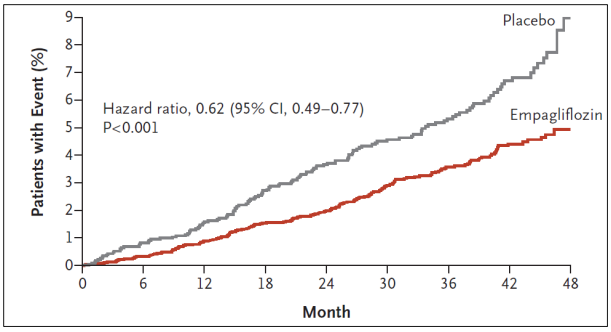
Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG 1⁰ Outcome (CV Death, Fatal/nonfatal MI & Stroke)



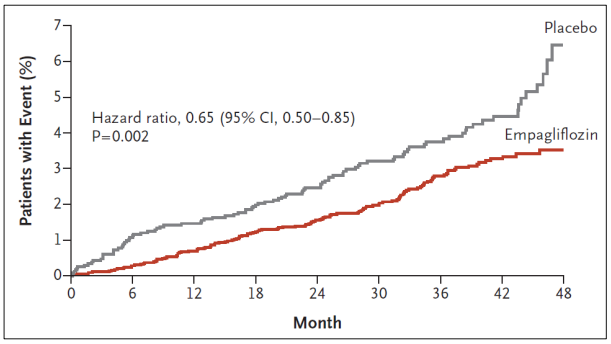
Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG: CV Death



Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG: Heart Failure Hospitalization



Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

CV Safety Trial Showing CV Risk REDUCTION Empagliflozin

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio * (95% CI)
	Empa	Pbo	
CV death, nonfatal MI & stroke	3.74	4.39	0.86 (0.74-0.99)
All cause mortality	1.94	2.86	0.68 (0.57-0.82)
CV death	1.24	2.02	0.62 (0.49-0.77)
HF hospitalization	0.94	1.45	0.65 (0.50-0.85)
HF hospitalization of CV death (excluding fatal stroke)	1.97	3.01	0.66 (0.55-0.79)

Zinman B et al *N Engl J Med*. 2015;373(22):2117-2128

CV Safety Trial Showing CV Risk REDUCTION Liraglutide

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio (95% CI) *
	Lira	Pbo	
CV death, nonfatal MI & stroke[a]	3.4	3.9	0.87 (0.78-0.97)
1⁰ + revascularization, unstable angina, or HF hospitalization	5.3	6.0	0.88 (0.81-0.96)
All cause mortality	2.1	2.5	0.85 (0.74-0.97)
CV death	1.2	1.6	0.78 (0.66-0.93)
Microvascular event	2.0	2.3	0.84 (0.73-0.97)
Nephropathy	1.86	3.06	0.78 (0.67-0.92)

Marso SP, et al. *N Engl J Med*. 2016;375(4):311-322.

CV Safety Trial Showing CV Risk REDUCTION Semaglutide (SQ)

Endpoint [a] = primary endpoint * p < 0.05	Rate/100 pt-years		Hazard Ratio (95% CI)
	Sema	Pbo	
CV death, nonfatal MI & stroke[a]	3.24	4.44	0.74 (0.58-0.95)*
1⁰ + revascularization, unstable angina, or HF hospitalization	6.17	8.36	0.74 (0.62-0.89)*
All cause mortality	1.82	1.76	1.05 (0.74-1.50)
CV mortality	1.29	1.35	0.98 (0.65-1.48)
Nonfatal stroke	0.80	1.31	0.61 (0.38-0.99)*
New or worsening nephropathy	1.86	3.06	0.64 (0.46-0.88)*

Marso SP, et al. *N Engl J Med*. 2016;375(19):1834-1844.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

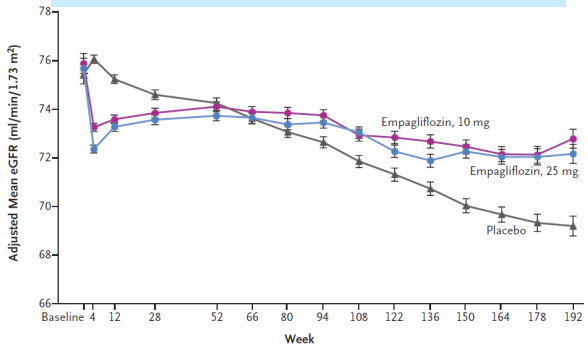
Wanner C et al *N Engl J Med* 2016;375(4):323-324

Empagliflozin: Renal Outcomes (EMPA-REG)

- Study: RDBPCT T2DM Adults (n=7,020)
- Rx: empagliflozin 10 or 25 mg qd
- Inclusion :
  - ASCVD +,GFR >30,BMI <45
- Outcomes:
  - Incident/worsening nephropathy (macroalbuminuria, 2X Cr, ESRD, renal death)
  - Incident albuminuria

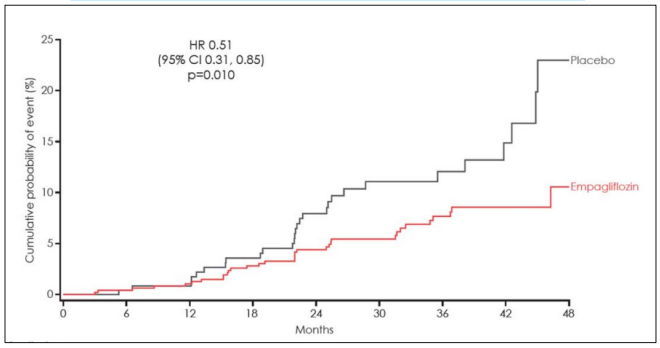
Wanner C et al *N Engl J Med* 2016;375(4):323-324

Emplagliflozin: Decline in GFR EMPA-REG



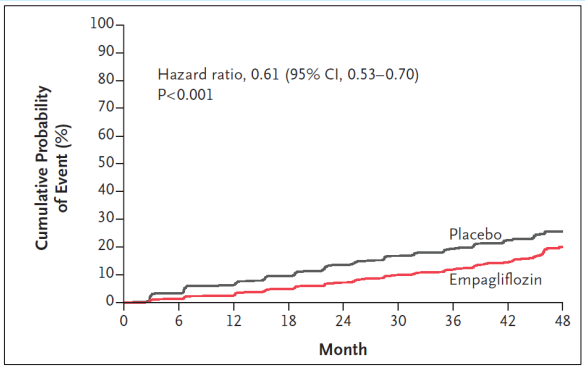
Wanner C et al *N Engl J Med* 2016;375(4):323-324

Emplagliflozin: 2X Cr EMPA-REG



Wanner C et al *N Engl J Med* 2016;375(4 Suppl Appendix):323-324

Empagliflozin: Incident/Worsening Nephropathy EMPA-REG Renal Results



Wanner C et al *N Engl J Med* 2016;375(4):323-324

Results of CV Outcomes Trials

	CV Safety	CV Benefit	Kidney Benefit
Dipeptidyl peptidase-4 inhibitors			
Alogliptin	✓		
Linagliptin	✓		
Saxagliptin	✓		✓
Sitagliptin	✓		
Glucagon-like peptide-1 receptor agonists			
Albiglutide*	✓	✓	
Dulaglutide	✓	✓	✓
Exenatide BID	NR		
Exenatide QW	✓		
Liraglutide	✓	✓	✓
Lixisenatide	✓		
Semaglutide	✓	✓	✓
Sodium glucose cotransporter-2 inhibitors			
Canagliflozin	✓	✓	✓
Dapagliflozin	✓	✓	✓
Empagliflozin	✓	✓	✓
Ertugliflozin	✓		

*No longer available as of December 2019.

Finerenone (Kerendia) Indications

"Kerendia is… indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, CV death, non-fatal MI, and hospitalization for heart failure in adult patients with CKD associated with T2DM."

Kerendia PI Revised 7/21

The CVD Stars

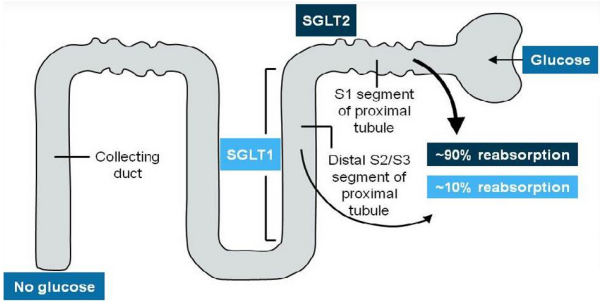
SGLT2-i

GLP1-RA

SGLT2 Inhibitors

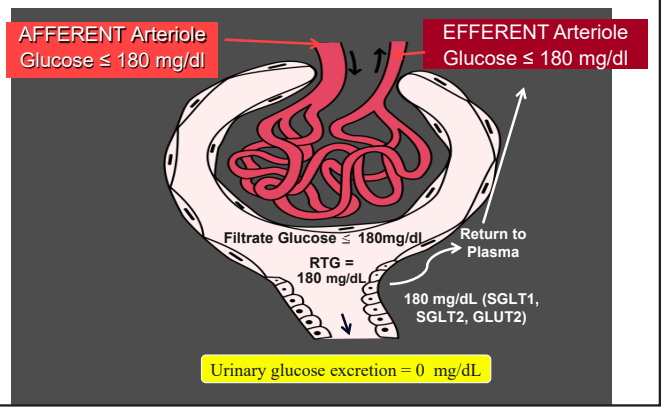
Canagliflozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)
Ertuglifozin (Steglatro)

Targeting the Kidney:SGLT2 Inhibition (Cana-, Dapa-,Empa-, Etrugliflozin)

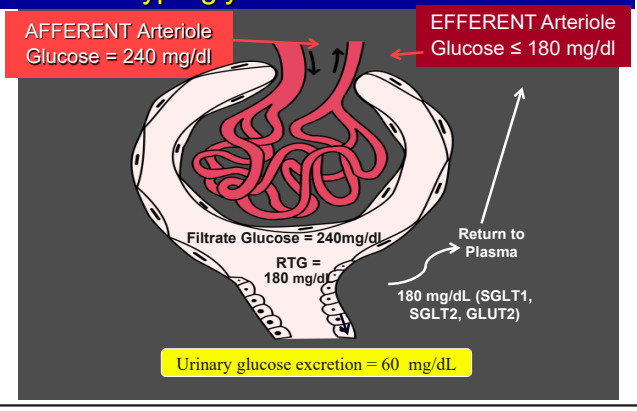


Adapted from Chao EC, et al. *Nat Rev Drug Discovery.* 2010;9:551-559.

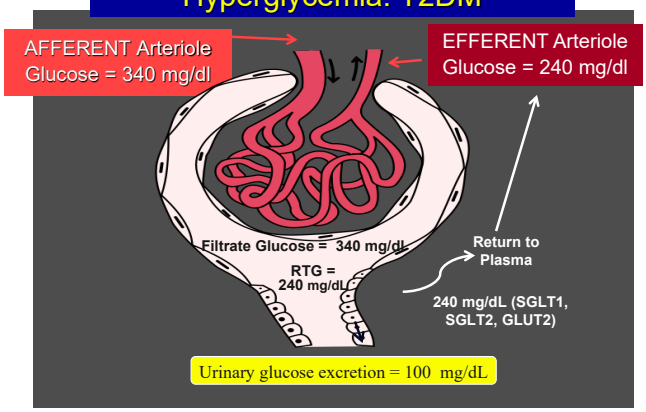
Normal Glucose: Normal RTG



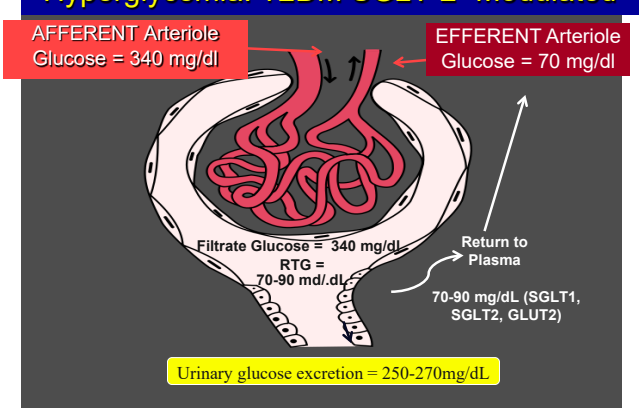
Hyperglycemia: Normal RTG



Hyperglycemia: T2DM



Hyperglycemia: T2DM SGLT-2- Modulated

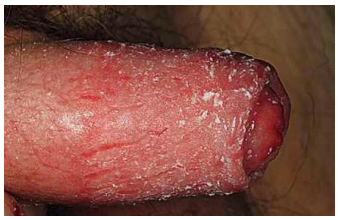


Safe Use of Flozins (SGLT2i)

AE	Cana	Dapa	Empa	Ertu
Hypotension	√	√	√	√
Ketoacidosis	√	√	√	√
AKI	√	√	√	√
UTI/Urosepsis	√	√	√	√
Hypoglycemia	√	√	√	√
Fournier's Gangrene	√	√	√	√
Amputations	√			√
Genital Mycotic Infections	√	√	√	√

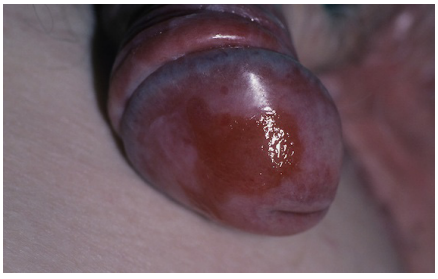
Source: Farxiga, Invokana, Jardiance, Steglatro PI

Candida Balanoposthitis



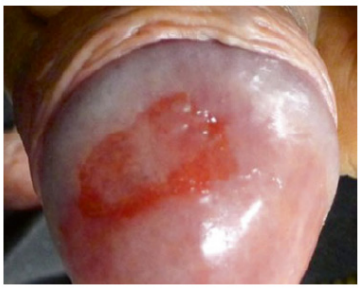
Dermnet.com accessed 2014 June

Candidal Balanitis



Dermnet.com accessed 2014 June

Erythroplasia of Queyrat
(CA in Situ)



Krasagakis K *European Handbook of Dermatological Treatments* Springer-Verlag Berlin Heidelberg 2015

Balanitis Rx

- Clotrimazole 1% cream b.i.d. X 1-3 weeks
- Miconazole 2% cream b.i.d. X 1-3 weeks
- Nystatin 100,000 u/g b.i.d. X 1-3 weeks
- Fluconazole 150 mg PO X 1

+

- Steroid cream if inflammation problematic

GLP1-RA

Exenatide (Byetta, Bydureon)
Liraglutide (Victoza, Saxenda)
Dulaglutide (Trulicity)
Lixisenatide (Adlyxin)
Semaglutide (Ozempic, Rybelsus)

The 'Magic' of GLP-1-RA
Physiologic Effects of GLP-1

- Blunted glucose-dependent glucagon secretion
- Augmented glucose-dependent insulin secretion
- Enhanced satiety
- Modulation of gastric emptying

Gallwitz B Int J Clin Pract 2006;60(12):1654-1661

SELF EVALUATION

New Directions in Type 2 Diabetes

1. An adult T2DM patient has CKD with albuminuria. What is the preferred initial treatment according to the ADA 2023 Pharmacology algorithm?
    a. An SGLT2 inhibitor (e.g., empagliflozin)
    b. A biguanide (e.g., metformin)
    c. A GLP1-RA (e.g., liraglutide)
    d. A sulfonylurea (e.g., glipizide)

2. A 60 y.o. patient with a history of MI one year ago has recently been diagnosed with T2DM. According to the ADA 2023 Guideline, which agent is preferred as first line pharmacotherapy for him?
    a. A sulfonylurea (e.g., glipizide)
    b. A TZD (e.g., pioglitazone)
    c. A GLP1-RA (e.g., liraglutide)

3. A 60 y.o. man is initiating treatment for recently diagnosed T2DM. He suffers from obesity, HTN, dyslipidemia, and smoking. What treatment is recommended for persons with this clinical constellation by the ADA 2023 pharmacologic treatment guideline?
    a. A sulfonylurea (e.g., glipizide)
    b. A GLP1-RA (e.g., exenatide)
    c. An SGLT2 (e.g., empagliflozin)

4. A 66 y.o. woman with T2DM has developed heart failure. Which agent is recommended by the ADA 2023 Pharmacologic Rx guideline to be part of her regimen?
    a. A sulfonylurea (e.g., glipizide)e.g., cyclobenzaprine)
    b. A TZD (e.g., pioglitazone)
    c. An SGLT2i (e.g., empagliflozin)

5. GLP1-RA agents (e.g., liraglutide) typically provide improvements in postprandial glucose excursions in T2DM. What is a mechanism for this effect?
    a. Blunting of glucagon
    b. Increased amylin secretion
    c. Blunting endogenous catecholamine secretion
    d. Inactivation of alpha-glucosidase

Answer Key: 1. A, 2. C, 3. C, 4. C, 5. A

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You may contact Mr. Ottenwess with you questions or comments at 313-965-2121, or by email at DOttenwess@OttenwessLaw.com.

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Anatomy of a Medical Malpractice Lawsuit - Parts 1 & 2

ANATOMY OF A LAWSUIT

What you don't know can hurt you.

The initial impact (Complaint filed)	Fight or flight (settle or proceed)	It's here – accept that it will be a part of your life for some time	The long game (settlement/trial /appeal)

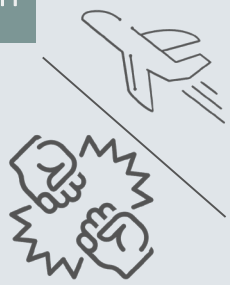
INITIAL IMPACT

- Don't panic
- Do not discuss with anyone (not out of shame, but strategy)
- Speak candidly to your attorney
- Pay attention and be patient
- Be prepared to participate

FIGHT OR FLIGHT

You are stuck…

- Early resolution
- Decide to proceed
  - Accept it
  - Participate
  - Prepare
  - Execute

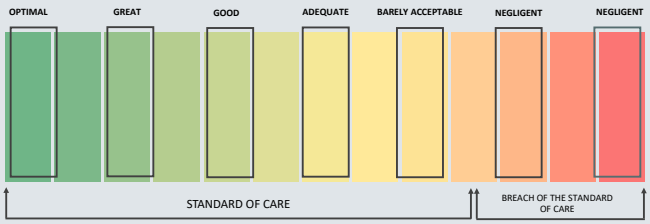


THE LAWSUIT

ELEMENTS OF A CASE

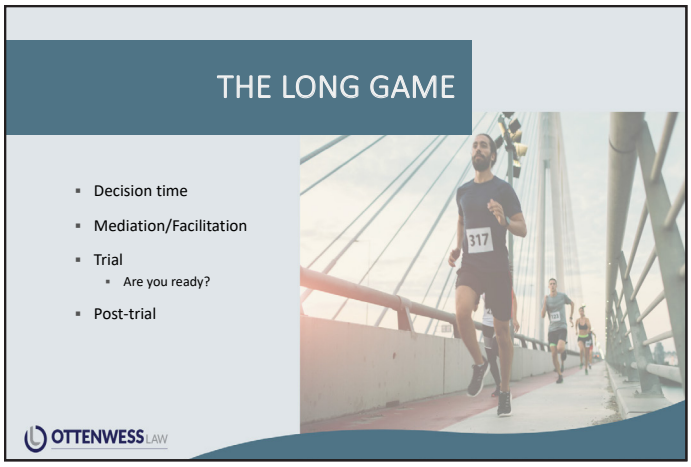
Duty	Causation
Breach of that duty	Injury/Damages

THE LAWSUIT CONTINUED



THE LAWSUIT CONTINUED

- Discovery
  - Depositions of parties
    - Your deposition is the most critical
- Experts
  - Cannot get to the jury without an expert to testify as to SOC and causation
  - These depositions are key. They…
    - Form legal basis for dismissal
    - Form basis for credibility attack


THE LONG GAME
Decision time
Mediation/Facilitation
Trial
Are you ready?
Post-trial
OTTENWESS LAW

SELF EVALUATION

Anatomy of a Medical Malpractice Lawsuit - Parts 1 & 2

1. When you receive notice of a lawsuit, you should immediately discuss your case with colleagues in order to line up a defense.

2. You should leave all decisions during the lawsuit to your attorney.

3. You should not prepare for a deposition or trial testimony because the truth will naturally flow from your testimony as you are the individual most knowledgeable about the facts.

4. Most cases resolve before trial.

5. If you know your case will settle, there is nothing to worry about.

6. Initially, you should keep the fact that you have a lawsuit to yourself and not discuss the matter with anyone except your insurance carrier and attorney (or family), but do not speak of it to others.

7. Getting to trial is a “piece of cake,” so no need to be bothered by the case during its pendency.

8. The standard of care by which a medical provider’s actions are judged in a medical malpractice case is whether he or she was able to provide the best care humanly possible.

9. Trial can be extremely stressful; therefore you must be ready to give your full concentration and best efforts to assist your case and the attorney at the proceedings.

10. Plaintiff’s attorneys are no match for the truth because that is what trial is all about: seeking and uncovering the truth.

Answer Key: 1. F, 2. F, 3. F, 4. T, 5. F, 6. T, 7. F, 8. F, 9. T, 10. F

C. Wayne Weart, Pharm.D., FASHP, FAPhA

C. Wayne Weart, PharmD, of Charleston, South Carolina, is professor emeritus of the Department of Clinical Pharmacy and Outcome Sciences at Medical University of South Carolina (MUSC) College of Pharmacy, as well as professor emeritus of Family Medicine in the College of Medicine, MUSC. Prior to MUSC he instructed at West Virginia University.

Dr. Weart has authored more than 100 publications and he has presented hundreds of hours of lectures to numerous professional groups and societies, medical and house staffs at both West Virginia University and MUSC, and national pharmacy and medical seminars across the country. He has received numerous awards and honors in his field including: "Outstanding Teacher" awards at both West Virginia University and MUSC; "Hospital Pharmacist of the Year" in both South Carolina and West Virginia; and designation as a Fellow of the American Society of Health Systems Pharmacists. In 1991 Dr. Weart was among the first pharmacists to become a board-certified pharmacotherapy specialist.

You may contact Dr. Weart with any questions or comments by email at weartcw@musc.edu.

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Pharmacotherapy Update - Parts 1-2

Use of Recombinant Zoster Vaccine in Immunocompromised Patients Aged ≥19 Years: MMWR / January 21, 2022 / Vol. 71 / No. 3 pp 80-84

- Dosing schedule. **Two RZV doses are necessary, regardless of previous history of herpes zoster or previous receipt of zoster vaccine live.** The **second RZV dose should typically be given 2–6 months after the first; for persons who are or will be immunodeficient or immunosuppressed and who would benefit from a shorter vaccination schedule, the second dose can be administered 1–2 months** after the first. If the second RZV dose is given sooner than 4 weeks after the first, a valid second dose should be repeated at least 4 weeks after the dose given too early. The vaccine **series does not need to be restarted if more than 6 months have elapsed since the first dose.**
- Timing of vaccination. **When possible, patients should be vaccinated before becoming immunosuppressed. Otherwise, providers should consider timing vaccination when the immune response is likely to be most robust** (i.e., during periods of lower immunosuppression and stable disease). RZV may be administered to patients who previously received varicella vaccine. RZV is not a live virus vaccine; therefore, **RZV may be administered while patients are taking antiviral medications.**
  - Concomitant administration of RZV with other adult vaccines has been studied, and there was no evidence for interference in the immune response to either vaccine or of safety concerns

Zoster Vaccine Recombinant, Adjuvanted (Shingrix)

Table 8. Efficacy of SHINGRIX on Incidence of Herpes Zoster Compared with Placebo in Immunocompromised Adults Aged ≥18 Years (mTVC[a])

Autologous, hematopoietic, stem cell transplant

Clinical Studies	Age Group (Years)	SHINGRIX N	SHINGRIX n	SHINGRIX Incidence Rate of HZ per 1,000 Person-Years	Placebo N	Placebo n	Placebo Incidence Rate of HZ per 1,000 Person-Years	% Efficacy (95% CI)
auHSCT[b]	Overall (≥18)[c]	870	49	30.0	851	135	94.3	68.2 (55.5, 77.6)
	18-49	213	9	21.5	212	29	76.0	71.8 (38.7, 88.3)
	≥50	657	40	33.0	639	106	100.9	67.3 (52.6, 77.9)

b Autologous, hematopoietic, stem cell transplant

Zoster Vaccine Recombinant, Adjuvanted (Shingrix)

- Efficacy in Subjects Aged 18 Years and Older with **Hematologic Malignancies - 515 subjects who received 2 doses of either Shingrix or placebo and did not develop a confirmed case of HZ within 1 month after the second dose.** Confirmed HZ cases were determined by either PCR (81.3%) or by a Clinical Evaluation Committee (18.7%). The post hoc analysis showed **Shringrix was 87.2%** (95% CI [44.2; 98.6]) **effective against development of HZ**. The **incidence rate of HZ per 1,000 person-years was 8.5 versus 66.2 in the Shingrix and placebo groups, respectively.**

Use of Recombinant Zoster Vaccine in Immunocompromised Adults Aged ≥19 Years: MMWR / January 21, 2022 / Vol. 71 / No. 3 pp 80-84

- **Pregnancy**. There is currently no ACIP recommendation for RZV use in pregnancy; therefore, **providers should consider delaying RZV until after pregnancy. There is no recommendation for pregnancy testing before vaccination.**
- **Breastfeeding**. Recombinant vaccines such as RZV pose no known risk to mothers who are breastfeeding or to their infants. Clinicians may **consider vaccination without regard to breastfeeding status if RZV is otherwise indicated.**
- Current episode of herpes zoster. RZV is not a treatment for herpes zoster or postherpetic neuralgia. **If a person is experiencing an episode of herpes zoster, vaccination should be delayed until the acute stage of the illness is over and symptoms abate.**

Human papillomavirus (HPV) recombinant 9-valent vaccine (Gardasil 9) Update

- **May 2021 The human papillomavirus (HPV) recombinant 9-valent vaccine (Gardasil 9)** received Food and Drug Administration (FDA) **accelerated approval for an expanded indication to include the prevention of oropharyngeal and other head and neck cancers** caused by HPV types 16, 18, 31, 33, 45, 52 and 58.
- **HPV DNA has been detected in approximately one-quarter of all head and neck cancers with HPV-16 present in approximately 90% of HPV-related oropharyngeal squamous cell carcinomas**, followed by HPV types 33, 35, and 58. HPV-related oropharyngeal squamous cell carcinoma is the most common HPV-related malignancy in the US. Non-Hispanic White male nonsmokers under the age of 64 years account for a majority of patients diagnosed with HPV-positive oropharyngeal squamous cell carcinomas.
  - **As required with accelerated approval, a post-approval confirmatory study is underway to evaluate the safety and efficacy of Gardasil 9 vaccination for prevention of persistent oropharyngeal HPV infection.** Analyses of the randomized, blinded, placebo-controlled trial will be driven by the number of oropharyngeal HPV-positive cases identified through polymerase chain reaction testing at six-month intervals. Once complete, the FDA will evaluate the study data to determine whether to grant traditional approval for this indication or remove the indication from the label.

Universal Hepatitis B Vaccination in Adults aged 19–59 Years: Updated Recommendations of the ACIP

MMWR / April 1, 2022 / 71(13);477–483

- **Recommendations - HepB vaccination is recommended for all adults aged 19–59 years and adults aged ≥60 years with risk factors for hepatitis B. Adults aged ≥60 years without known risk factors for hepatitis B may also receive HepB vaccines**. Infants and all other persons aged <19 years are already recommended to receive HepB vaccines.
  - Rates of reported acute hepatitis B have not notably decreased for over 1 decade, with 20,700 estimated infections in 2019.
  - The safety of single-antigen 3-dose HepB vaccines has been established. Pre-Hevbrio was approved by FDA in 2021 and recommended by ACIP in 2022. Little or no difference in seroprotection or occurrence of serious adverse events or mild adverse events (GRADE evidence type 3; low certainty evidence) was found for PreHevbrio in comparison with a 3-dose, single-antigen vaccine (Engerix-B), and serious adverse events were rare for both vaccines. The 2-dose HepB vaccine (Heplisav-B) was approved by FDA in 2017 and recommended by ACIP in 2018. No difference in occurrence of serious adverse events (GRADE evidence type 1; high certainty evidence) was found for Heplisav-B compared with a 3-dose vaccine (Engerix-B), and serious adverse events were rare for both vaccines.

Updated Recommendations of the Advisory Committee on Immunization Practices — MMWR / January 28, 2022 / 71(4);109–117

New Pneumococcal Vaccine Recommendations

- **Adults aged ≥65 years who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.**
- **Adults aged 19–64 years with certain underlying medical conditions or other risk factors who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.**
  - **When PCV15 is used, the recommended interval between administration of PCV15 and PPSV23 is ≥1 year. A minimum interval of 8 weeks can be considered for adults with an immunocompromising condition,** cochlear implant, or cerebrospinal fluid leak to minimize the risk for IPD caused by serotypes unique to PPSV23 in these vulnerable groups.

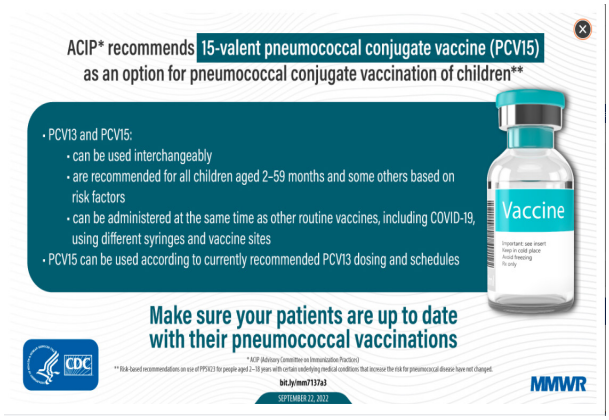
Updated Recommendations of the Advisory Committee on Immunization Practices — MMWR / January 28, 2022 / 71(4);109–117

- **Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23.**
- **Adults with previous PCV13. The incremental public health benefits of providing PCV15 or PCV20 to adults who have received PCV13 only or both PCV13 and PPSV23 have not been evaluated. These adults should complete the previously recommended PPSV23.**
  - Coadministration with other vaccines. PCV15, PCV20, or PPSV23 can be coadministered with QIV in an adult immunization program, as **concomitant administration (PCV15 or PPSV23 and QIV [Fluarix], PCV20 and adjuvanted QIV [Fluad]) has been demonstrated to be immunogenic and safe**. However, slightly lower pneumococcal serotype-specific OPA GMTs or geometric mean concentrations were reported when pneumococcal vaccines were coadministered with QIV compared with when pneumococcal vaccines were given alone. Currently, no data are available on coadministration with other vaccines (e.g., tetanus, diphtheria, acellular pertussis vaccine, hepatitis B, or zoster vaccine) among adults. **Evaluation of coadministration of PCV15, PCV20, or PPSV23 with COVID-19 vaccines is ongoing.**

TABLE 1. Recommendations for use of 15-valent pneumococcal conjugate vaccine in series with 23-valent pneumococcal polysaccharide vaccine or 20-valent pneumococcal conjugate vaccine in pneumococcal conjugate vaccine–naïve adults aged ≥19 years — United States, 2022

Medical indication group	Specific underlying medical condition	Age group, yrs	
		19–64	≥65
None	None	None	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later*
Underlying medical conditions or other risk factors	Alcoholism Chronic heart disease† Chronic liver disease Chronic lung disease¶ Cigarette smoking Diabetes mellitus Cochlear implant CSF leak Congenital or acquired asplenia Sickle cell disease or other hemoglobinopathies Chronic renal failure** Congenital or acquired immunodeficiencies**,†† Generalized malignancy** HIV infection** Hodgkin disease** Iatrogenic immunosuppression**,§§ Leukemia** Lymphoma** Multiple myeloma** Nephrotic syndrome** Solid organ transplant**	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later§	1 dose of PCV20 or 1 dose of PCV15 followed by a dose of PPSV23 ≥1 years later*

MMWR / January 28, 2022 / Vol. 71 / No. 4 113



ACIP Meeting 6/22-23/2022

- The **committee voted 15-0 to recommend that people aged 65 years or older receive a high-dose inactivated influenza vaccine, adjuvanted inactivated influenza vaccine, or recombinant influenza vaccine over any of the standard-dose unadjuvanted, inactivated vaccines.**
- **The committee also voted unanimously to recommend Vaxneuvance (PCV15) for children. Merck's 15-valent pneumococcal vaccine was approved by the FDA for infants and children aged 6 weeks to 17 years.**
  - **The immune responses elicited by PCV15 following a four-dose pediatric series were noninferior to the currently available 13-valent pneumococcal conjugate vaccine (PCV13). They determined that both vaccines will be recommended as a 4-dose series at 2, 4, 6, and 12 to 15 months and that the two can be used interchangeably.**
- **The committee gave the green light to a second MMR vaccine, Priorix (GSK), for use as an option in the U.S. in people aged 6 months or older. Previously, only Merck's MMR vaccine was available.**

PCV-20 – Prevnar 20 Update

- The U.S. **Food and Drug Administration granted priority review and accepted the supplemental Biologics License Application for PCV-20 to prevent invasive pneumococcal disease caused by the 20 Streptococcus pneumoniae (pneumococcus) serotypes contained in the vaccine in infants and children 6 weeks through 17 years of age, and for preventing otitis media caused by seven of the 20 Streptococcus pneumoniae serotypes contained in the vaccine. (PCV-20 had previously received the FDA's fast track and breakthrough therapy designations for the pediatric indication for IPD).**
- The **FDA is expected to make a decision on the sBLA by April 2023.**
- Under priority review, the FDA's goal is to take action within six months, compared to 10 months under standard review.
- The sBLA was backed by data from phase 3 and phase 2 trial programs for the pediatric indication for PCV-20.

Update on Efficacy of the 2022-23 Flu Vaccines

- **This year's influenza vaccine is "a very good match" to the strains currently circulating, Rochelle Walensky, MD, director of the Centers for Disease Control and Prevention** (CDC), said in a press briefing on December 5.
- **Hospitalizations from the flu, however, are continuing to climb to dangerous levels, likely due to low vaccination rates and people choosing not to mask or to stay home when they're feeling sick**, experts said.
  - Transcript: CDC Media Telebriefing – Update on Respiratory Disease Circulation 12-5-2022

Update on COVID Vaccines

- Oct 20, 2022- An independent panel of experts at the Centers for Disease Control and Prevention (CDC) endorsed that **COVID-19 vaccines should be added to the agency's regular immunizations recommended for children and adults.**
- CDC's **Advisory Committee on Immunization Practices (ACIP) voted in favor of the move, which will see COVID-19 vaccines becoming part of the regular immunizations such as measles and tetanus vaccines that U.S. adults and children aged six months and older are recommended to get.**

COVID-19 Vaccine
Interim COVID-19 Immunization Schedule for Persons 6 Months of Age and Older

12/08/2022

Table 1a. **Moderna: Immunization Schedule for Children 6 Months through 17 Years of Age**

Age*	For Most People		Those Who **ARE** Moderately or Severely Immunocompromised	
	Doses	Interval Between Doses†	Doses	Interval Between Doses
6 months through 5 years	**Primary series‡: MONOVALENT VACCINE** (Blue capped vial with magenta-bordered label)			
	Dose 1 to 2	At least 4–8 weeks§	Dose 1 to 2	At least 4 weeks
			Dose 2 to 3	At least 4 weeks
	Booster dose¶: BIVALENT VACCINE (Dark pink capped vial with yellow-bordered label)			
	Dose 2 to 3	At least 8 weeks (2 months)	Dose 3 to 4	At least 8 weeks (2 months)
6 through 11 years	**Primary series**: MONOVALENT VACCINE** (Blue capped vial with purple-bordered label)			
	Dose 1 to 2	At least 4–8 weeks§	Dose 1 to 2	At least 4 weeks
			Dose 2 to 3	At least 4 weeks
	Booster dose: BIVALENT VACCINE (Blue capped vial with gray-bordered label)			
	Dose 2 to 3	At least 8 weeks (2 months)	Dose 3 to 4	At least 8 weeks (2 months)
12 through 17 years	**Primary series††: MONOVALENT VACCINE** (Red capped vial with blue-bordered label)			
	Dose 1 to 2	At least 4–8 weeks§	Dose 1 to 2	At least 4 weeks
			Dose 2 to 3	At least 4 weeks
	Booster dose: BIVALENT VACCINE (Blue capped vial with gray-bordered label)			
	Dose 2 to 3	At least 8 weeks (2 months)	Dose 3 to 4	At least 8 weeks (2 months)

† Persons with a recent SARS-CoV-2 infection may consider delaying a primary series or booster dose by 3 months from symptom onset or positive test (if infection was asymptomatic)

§ An 8-week interval between the first and second primary series doses of Moderna, Novavax, and Pfizer-BioNTech COVID-19 vaccines may be optimal for some people ages 6 months–64 years, especially for males ages 12–39 years, as it may reduce the small risk of myocarditis and pericarditis associated with these vaccines.

The authorized interval (**4 weeks for Moderna COVID-19Vaccine) between the first and second doses remains the recommended interval for people who are moderately or severely immunocompromised; adults ages 65 years and older; and in situations in which there is increased concern about COVID-19 community levels or an individual's higher risk of severe disease.**

COVID-19 Vaccine
Interim COVID-19 Immunization Schedule for Persons 6 Months of Age and Older

12/08/2022

Table 1b. **Pfizer-BioNTech: Immunization Schedule for Children 6 Months through 17 Years of Age**

Age*	For Most People		Those Who **ARE** Moderately or Severely Immunocompromised	
	Doses	Interval Between Doses†	Doses	Interval Between Doses
6 months through 4 years	**Primary series‡: MONOVALENT VACCINE - Doses 1 and 2** (Maroon capped vial with maroon-bordered label) and **BIVALENT VACCINE - Dose 3** (Maroon capped vial with maroon-bordered label)			
	Dose 1 to 2	At least 3–8 weeks§	Dose 1 to 2	At least 3 weeks
	Doses 2 and 3	At least 8 weeks (2 months)	Dose 2 to 3	At least 8 weeks
5 through 11 years	**Primary series¶: MONOVALENT VACCINE** (Orange capped vial with orange-bordered label)			
	Dose 1 to 2	At least 3–8 weeks§	Dose 1 to 2	At least 3 weeks
			Dose 2 to 3	At least 4 weeks
	Booster dose: BIVALENT VACCINE (Orange capped vial with orange-bordered label)			
	Dose 2 to 3	At least 8 weeks (2 months)	Dose 3 to 4	At least 8 weeks (2 months)
12 years through 17 years	**Primary series**: MONOVALENT VACCINE** (Gray capped vial with gray-bordered label)			
	Dose 1 to 2	At least 3-8 weeks§	Dose 1 to 2	At least 3 weeks
			Dose 2 to 3	At least 4 weeks
	Booster dose: BIVALENT VACCINE (Gray capped vial with gray-bordered label)			
	Dose 2 to 3	At least 8 weeks (2 months)	Dose 3 to 4	At least 8 weeks (2 months)

† Persons with a recent SARS-CoV-2 infection may consider delaying a primary series or booster dose by 3 months from symptom onset or positive test (if infection was asymptomatic)

§ An 8-week interval between the first and second primary series doses of Moderna, Novavax, and Pfizer-BioNTech COVID-19 vaccines may be optimal for some people ages 6 months–64 years, especially for males ages 12–39 years, as it may reduce the small risk of myocarditis and pericarditis associated with these vaccines.

COVID-19 Vaccine
Interim COVID-19 Immunization Schedule for Persons 6 Months of Age and Older

Table 1c. **Novavax: Immunization Schedule for Children 6 Months through 17 Years of Age** 12/08/2022

Age*	For Most People		Those Who **ARE** Moderately or Severely Immunocompromised	
	Doses	Interval Between Doses†	Doses	Interval Between Doses
12 years and older	**Primary series‡: MONOVALENT VACCINE**			
	Dose 1 to 2	At least 3–8 weeks§	Dose 1 to 2	At least 3 weeks
	Booster dose: BIVALENT mRNA VACCINE Moderna or Pfizer-BioNTech bivalent COVID-19 vaccine should be used for the booster dose.			
	Dose 2 to 3	At least 8 weeks (2 months)	Dose 2 to 3	At least 8 weeks (2 months)

§ An 8-week interval between the first and second primary series doses of Moderna, Novavax, and Pfizer-BioNTech COVID-19 vaccines may be optimal for some people ages 6 months–64 years, especially for males ages 12–39 years, as it may reduce the small risk of myocarditis and pericarditis associated with these vaccines.

COVID-19 Vaccine
Interim COVID-19 Immunization Schedule for Persons 6 Months of Age and Older

12/08/2022

Table 2. **Immunization Schedule for Persons 18 Years of Age**

Type	Age	For Most People		Those Who **ARE** Moderately or Severely Immunocompromised	
		Doses	Interval Between Doses*	Doses	Interval Between Doses
Moderna	18 years and older	**Primary series†: MONOVALENT VACCINE** (Red capped vial with a blue-bordered label)			
		Dose 1 to 2	At least 4–8 weeks‡	Dose 1 to 2	At least 4 weeks
				Dose 2 to 3	At least 4 weeks
		Booster dose§: BIVALENT VACCINE (Blue capped vial with a gray-bordered label)			
		Dose 2 to 3	At least 8 weeks (2 months)	Dose 3 to 4	At least 8 weeks (2 months)
Pfizer-BioNTech	18 years and older	**Primary series†: MONOVALENT VACCINE** (Gray capped vial with a gray-bordered label)			
		Dose 1 to 2	At least 3-8 weeks‡	Dose 1 to 2	At least 3 weeks
				Dose 2 to 3	At least 4 weeks
		Booster dose§: BIVALENT VACCINE (Gray capped vial with a gray-bordered label)			
		Dose 2 to 3	At least 8 weeks (2 months)	Dose 3 to 4	At least 8 weeks (2 months)
Novavax	18 years and older	**Primary series†: MONOVALENT VACCINE**			
		Dose 1 to 2	At least 3–8 weeks‡	Dose 1 to 2	At least 3 weeks
		Booster dose§: BIVALENT VACCINE Moderna or Pfizer-BioNTech bivalent COVID-19 vaccine should be used for the booster dose.			
		Dose 2 to 3	At least 8 weeks (2 months)	Dose 2 to 3	At least 8 weeks (2 months)
Janssen	18 years and older	**Primary series: MONOVALENT VACCINE** Janssen COVID-19 vaccine is authorized for use in certain limited situations due to safety considerations.¶			
		Booster dose§: BIVALENT mRNA VACCINE Moderna or Pfizer-BioNTech bivalent COVID-19 vaccine should be used for the booster dose.			
		Administer a single booster dose at least 8 weeks (2 months) after the previous dose.			

† Persons with a recent SARS-CoV-2 infection may consider delaying a primary series or booster dose by 3 months from symptom onset or positive test (if infection was asymptomatic)

§ An 8-week interval between the first and second primary series doses of Moderna, Novavax, and Pfizer-BioNTech COVID-19 vaccines may be optimal for some people ages 6 months–64 years, especially for males ages 12–39 years, as it may reduce the small risk of myocarditis and pericarditis associated with these vaccines.

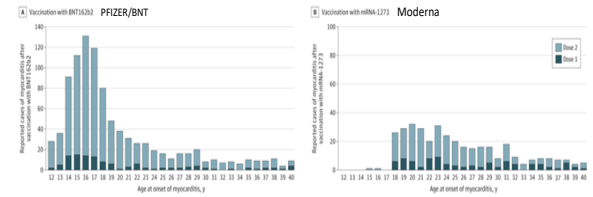
The authorized interval (4 weeks for Moderna COVID-19Vaccine) between the first and second doses remains the recommended interval for people who are moderately or severely immunocompromised; adults ages 65 years and older; and in situations in which there is increased concern about COVID-19 community levels or an individual's higher risk of severe disease.

COVID-19 Vaccines and Myocarditis and Pericarditis

- After reviewing available data on the risks and benefits, **ACIP and CDC determined that the benefits (e.g., prevention of COVID-19 and its severe outcomes) outweigh the rare risk of myocarditis and pericarditis after receipt of Moderna, Novavax, and Pfizer-BioNTech COVID-19 vaccines** in all populations for which vaccination has been recommended.
- **Extending the interval to 8 weeks between the first and second primary series doses of Moderna, Novavax, or Pfizer-BioNTech COVID-19 vaccines for some people may reduce the rare risk of vaccine-associated myocarditis and pericarditis.**
- **People receiving Moderna, Novavax, and Pfizer-BioNTech COVID-19 vaccines, especially males ages 12–39 years, should be made aware of the rare risk of myocarditis and pericarditis following receipt of these vaccines, symptoms include chest pain, shortness of breath, or tachycardia develop after vaccination, particularly in the week after vaccination.**

COVID-19 Vaccines and Myocarditis and Pericarditis

Figure 1. Cases of Myocarditis After mRNA-Based COVID-19 Vaccination by Age at Onset of Myocarditis



The reports to the Vaccine Adverse Event Reporting System met the case definition of myocarditis (reported cases). Among individuals older than 40 years of age, there were no more than 8 reports of myocarditis for any individual age after receiving either vaccine. For the BNT162b2 vaccine, there were 114 246 837 first vaccination doses and 95 532 396 second vaccination doses; and for the mRNA-1273 vaccine, there were 78 158 611 and 66 163 001, respectively. The y-axis range differs between panels A and B.

JAMA. 2022;327(4):331-340. doi:10.1001/jama.2021.24110

COVID-19 Vaccines and Myocarditis and Pericarditis

Table 2. Reports to VAERS After mRNA-Based COVID-19 Vaccination That Met the CDC's Case Definition for Myocarditis Within a 7-Day Risk Interval per Million Doses of Vaccine Administered

	Reported cases of myocarditis within a 7-d risk interval per million doses of vaccine administered (95% CI)[a]				Expected cases of myocarditis in a 7-d risk interval per million doses (95% CI)[b]
	Vaccination with BNT162b2		Vaccination with mRNA-1273[b]		
	First dose	Second dose	First dose	Second dose	
Males					
Age group, y					
12-15	7.06 (4.88-10.23)	70.73 (61.68-81.11)			0.53 (0.40-0.70)
16-17	7.26 (4.45-11.86)	105.86 (91.65-122.27)			1.34 (1.05-1.72)
18-24	3.82 (2.40-6.06)	52.43 (45.56-60.33)	10.73 (7.50-15.34)	56.31 (47.08-67.34)	1.76 (1.58,1.98)
25-29	1.74 (0.78-3.87)	17.28 (13.02-22.93)	4.88 (2.70-8.80)	24.18 (17.93-32.61)	1.45 (1.21-1.74)
30-39	0.54 (0.20-1.44)	7.10 (5.26-9.57)	3.00 (1.81-4.97)	7.93 (5.61-11.21)	0.63 (0.54,0.73)
40-49	0.55 (0.21-1.48)	3.50 (2.28-5.36)	0.59 (0.19-1.82)	4.27 (2.69-6.78)	0.78 (0.67-0.90)
50-64	0.42 (0.17-1.01)	0.68 (0.33-1.43)	0.62 (0.28-1.39)	0.85 (0.41-1.79)	0.77 (0.68-0.86)
≥65	0.19 (0.05-0.76)	0.32 (0.10-1.00)	0.18 (0.05-0.72)	0.51 (0.21-1.23)	
Females					
Age group, y					
12-15	0.49 (0.12-1.98)	6.35 (4.05-9.96)			0.17 (0.11-0.29)
16-17	0.84 (0.21-3.37)	10.98 (7.16-16.84)			0.42 (0.27-0.66)
18-24	0.18 (0.03-1.31)	4.12 (2.60-6.54)	0.96 (0.31-2.96)	6.87 (4.27-11.05)	0.38 (0.30-0.49)
25-29	0.26 (0.04-1.84)	2.23 (1.07-4.69)	0.41 (0.06-2.94)	8.22 (5.03-13.41)	0.48 (0.35-0.65)
30-39	0.72 (0.32-1.60)	1.02 (0.49-2.14)	0.74 (0.28-1.98)	0.68 (0.22-2.10)	0.47 (0.39-0.57)
40-49	0.24 (0.06-0.97)	1.73 (0.98-3.05)	0.18 (0.02-1.25)	1.89 (0.98-3.63)	0.89 (0.77-1.04)
50-64	0.37 (0.15-0.88)	0.51 (0.23-1.14)	0.65 (0.31-1.36)	0.43 (0.16-1.15)	1.00 (0.89-1.13)
≥65	0.08 (0.01-0.54)	0.35 (0.13-0.92)		0.26 (0.08-0.81)	

JAMA. 2022;327(4):331-340. doi:10.1001/jama.2021.24110

SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents

- **Data on 23 million people from Scandinavia that include both the Pfizer and Moderna vaccines shows a clearly higher risk of myocarditis after the Moderna vaccine than after the Pfizer vaccine**. This has been suggested before, but our data confirm definitively that the Moderna vaccine has a higher risk of myocarditis than the Pfizer vaccine.
- **"In the group at highest risk of myocarditis after COVID vaccination — young men aged 16 to 24 — the Pfizer vaccine shows a five times higher risk of myocarditis versus the unvaccinated cohort, while the Moderna vaccine shows a 15 times higher risk,"** (Rickard Ljung, MD, Swedish Medical Products Agency)
- **After seeing these data, the Swedish regulatory authority is no longer recommending use of the Moderna vaccine for people younger than 30 years, Ljung said. Similar recommendations have been made in Norway and Finland.**
  - JAMA Cardiol. 2022;7(6):600-612. doi:10.1001/jamacardio.2022.0583

COVID-19 Vaccines

- **1-26-2023 A panel of independent experts that advises the US Food and Drug Administration on its vaccine decisions voted unanimously to update all Covid-19 vaccines, so they contain the same ingredients as the two-strain shots that are now used as booster doses.**
- The **vote means young children and others who haven't been vaccinated may soon be eligible to receive two-strain vaccines that more closely match the circulating viruses as their primary series.**
- The FDA must sign off on the committee's recommendation, which it is likely to do, before it goes into effect.

CDC Working Group on Covid-19 Vaccines

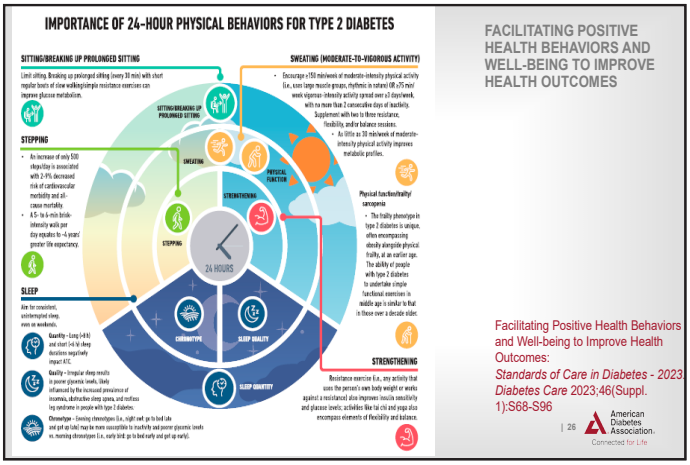
Considerations for Bivalent Primary Series

Summary **ACIP Meeting February 24, 2023**

- Receiving a **COVID-19 vaccine primary series** continues to be important for prevention of COVID-19 severe disease, hospitalization, and death
- Many children and adolescents remain unvaccinated for COVID-19
- COVID-19 vaccines recommendations that are **simple to implement** may remove some barriers to uptake
- Harmonizing the primary series and booster doses could simplify the presentations, reduce administration errors, and allow continued access to primary series for unvaccinated populations
- The Work Group was **supportive** of a transition of the mRNA COVID-19 vaccine primary series from monovalent (original) to bivalent (original plus Omicron BA.4/5)

Standards of Care in Diabetes—2023

American Diabetes Association. Connected for Life



Importance of 24-h physical behaviors for type 2 diabetes

	Glucose/insulin	Blood pressure	HbA_{1c}	Lipids	Physical function	Depression	Quality of life
SITTING/BREAKING UP PROLONGED SITTING	↓	↓	↓	↓	↑	↓	↑
STEPPING	↓	↓	↓	↓	↑	↓	↑
SWEATING (MODERATE-TO-VIGOROUS ACTIVITY)	↓	↓	↓	↓	↑	↓	↑
STRENGTHENING	↓	↓	↓	↓	↑	↓	↑
ADEQUATE SLEEP DURATION	↓	↓	↓	↓	?	↓	↑
GOOD SLEEP QUALITY	↓	↓	↓	↓	?	↓	↑
CHRONOTYPE/CONSISTENT TIMING	↓	?	↓	?	?	↓	?

IMPACT OF PHYSICAL BEHAVIORS ON CARDIOMETABOLIC HEALTH IN PEOPLE WITH TYPE 2 DIABETES

↑ **Higher levels/improvement** (physical function, quality of life); ↓ **Lower levels/improvement** (glucose/insulin, blood pressure, HbA_{1c}, lipids, depression); ? no data available;
↑ Green arrows = **strong evidence**; ↑ Yellow arrows = **medium strength evidence**; ↑ Red arrows = **limited evidence**.

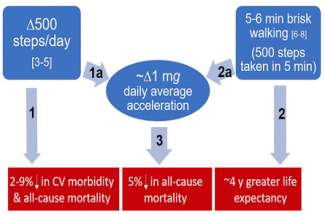
Diabetes Care 2023;46(Suppl. 1):S68-S96

Sedentary time and activity breaks

- **In adults with T2D, the interruption of prolonged sitting with activity breaks, such as light-intensity walking or simple resistance activities for 3 min every 30 min over 8 h, decreases postprandial glucose, insulin, C-peptide, and triglyceride levels.**
  - Diabetes Care. 2016;39(6):964–72.
- **Short 5-min breaks every h over 12 h more effectively lowered glucose and insulin levels than 1 h of moderate-intensity continuous exercise at the beginning of the day in people with impaired glucose tolerance.**
  - Metabolism. 2014;63(4):510–9.

Steps and Mortality

3-Lancet 2014;383:1059–66
4- JAMA Intern Med 2019;179:1105–12
5-JAMA 2020;323:1151–60



6-JAMA. 2018;320(19):2020-2028
7-Med Sci Sports Exerc 2018;50:1323–32.
8-BMC Med 2019;17:108

Figure 1 Converging evidence for a preliminary estimation of the MCID in mg for inactive people. (1) An increase or difference of 500 steps per day, is associated with a 2% to 9% decreased risk of cardiovascular morbidity and all-cause mortality.3–5 (1a) A change in 500 steps per day approximates a change in average acceleration of 0.8 mg. (2) A daily 5 to 6min brisk walk is associated with a greater life expectancy of 3.9 years.8 (2a) This would increase daily average acceleration by approximately 0.8 to 1.0mg (based on a 5 to 6min brisk walk replacing time spent at the average acceleration, as described in Rowlands et al, 7 and a brisk walk eliciting an acceleration of 250 mg, 8. (3) Estimated from UK Biobank data. Higher average acceleration (per 1 mg) was associated with lower all-cause mortality HR=0.95 (95% CI; 0.94 to 0.96). CV, cardiovascular; MCID, minimum clinically important difference; mg, milli-gravitational units.

Br J Sports Med July 2021 Vol 55 No 14

Steps and Mortality

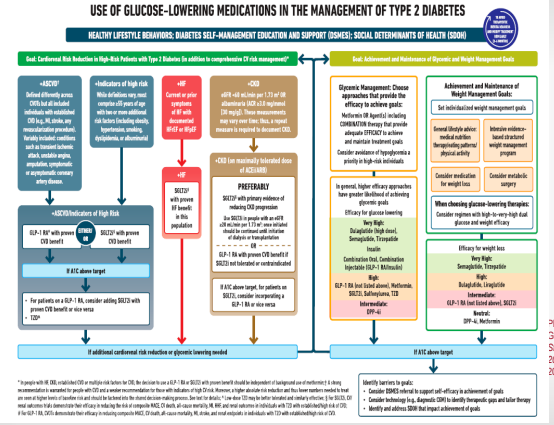
- **Taking more steps per day is associated with a progressively lower risk for cardiovascular disease (CVD) among older adults, and the benefits accrue at well below the widely promoted threshold of 10,000 steps per day, new research shows.**
- Among **adults aged 60 years and older, those who took roughly 6000 to 9000 steps per day had a 40% to 50% lower risk for CVD compared with peers logging just 2000 steps per day.**
- **Survival curves among older adults showed that cardiovascular risk declined sharply as daily steps increased from 1000 to 5000, with a milder decrease between 5000 and 15,000 steps.**
  - Paluch AE, et al. Prospective association of daily steps with cardiovascular disease: a harmonized meta-analysis. Circulation. 2023;147(2):122-131.

Sleep and HbA1c in Patients With Type 2 Diabetes

- **The quantity of sleep is known to be associated (in a U-shaped manner) with health outcomes (e.g., obesity and HbA1c), with both long (>8 h) and short (<6 h) sleep durations having negative impacts. By extending the sleep duration of short sleepers, it is possible to improve insulin sensitivity and reduce energy intake.**
  - **Sleep Med Rev 2017;31: 91–101**
- **Total sleep duration was significantly associated with HbA1c in a U-shaped manner, indicating worse glycemic control with both short and long sleep compared with sleep medium duration, with the nadir at 436 min (7 h 16 min).**
- Sleep efficiency, variability in sleep duration, variability in midsleep time, and subjective sleep quality were significantly associated with HbA1c, with **higher HbA1c in individuals with lower efficiency, higher variability, and worse quality.**
  - Diabetes Care 2020;43:235–243

Exercise effects on A1c and exercise volume in patients with Type 2 diabetes

- Beneficial effects of exercise are evident across the continuum of human movement, from breaking prolonged sitting with light activity to high-intensity interval training.
  - Ann Phys Rehabil Med 2022; 65:101586
- **Interventions with combined aerobic and resistance exercise training may be superior to either mode alone. A greater reduction in A1C has been noted in adults with T2D undertaking a combined training program compared with either type alone, and combined training group participants had a greater exercise volume.**
  - Ann Intern Med. 2007;147(6):357–69
- **In another trial, combined training significantly improved A1C levels over non-exercising controls, although neither resistance nor aerobic training alone resulted in significant changes.**
  - . JAMA. 2010;304(20):2253–62.



Pharmacologic Approaches to Glycemic Management: *Standards of Care in Diabetes - 2023. Diabetes Care* 2023;46(Suppl. 1):S140-S157

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Pharmacologic Therapy for Adults With Type 2 Diabetes

9.4a Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. A

9.4b In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (Fig. 9.3 and Table 9.2). A

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

9.4c **Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy** (Fig. 9.3 and Table 9.2).. E

9.4d Weight management is an impactful component of glucose-lowering management in type 2 diabetes. **The glucose-lowering treatment regimen should consider approaches that support weight management goals** (Fig. 9.3 and Table 9.2). A

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

9.5 **Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits.** A

9.6 Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. A

9.7 **The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300mg/dL [16.7mmol/L]) are very high.** E

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

9.8 A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences (Fig. 9.3 and Table 9.2). **E**

9.9 **Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit** (Fig. 9.3, Table 9.2, Table 10.3B, and Table 10.3C) **is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors** (Fig. 9.3) (see Section 10, "Cardiovascular Disease and Risk Management," for details on cardiovascular risk reduction recommendations). **A**

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

Pharmacologic Therapy for Adults With Type 2 Diabetes (continued)

9.10 **In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. A**

9.11 **If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. A**

9.12 Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. **A**

Table 9.2—Medications for lowering glucose, summary of characteristics

	Efficacy[1]	Hypoglycemia	Weight change[2]	CV effects		Renal effects		Oral/SQ	Cost	Clinical considerations
				Effect on MACE	HF	Progression of DKD	Dosing/use considerations[3]			
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Neutral	• Contraindicated with eGFR <30 mL/min per 1.73 m²	Oral	Low	• GI side effects common; to mitigate GI side effects, consider slow dose titration, extended release formulations, and administration with food • Potential for vitamin B12 deficiency; monitor at regular intervals
SGLT2 inhibitors	Intermediate to high	No	Loss (intermediate)	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Benefit: canagliflozin, dapagliflozin, empagliflozin	• See labels for renal dose considerations of individual agents • Glucose-lowering effect is lower for SGLT2 inhibitors at lower eGFR	Oral	High	• DKA risk; rare in T2DM; discontinue, evaluate, and treat promptly if suspected; be aware of predisposing risk factors and clinical presentation (including euglycemic DKA); discontinue before scheduled surgery (e.g., 3–4 days); during critical illness, or during prolonged fasting to mitigate potential risk • Increased risk of genital mycotic infections • Necrotizing fasciitis of the perineum (Fournier gangrene), rare reports: institute prompt treatment if suspected • Attention to volume status, blood pressure; adjust other volume-contracting agents as applicable
GLP-1 RAs	High to very high	No	Loss (intermediate to very high)	Benefit: dulaglutide, liraglutide, semaglutide (SQ) Neutral: exenatide once weekly, lixisenatide	Neutral	Benefit for renal endpoints in CVOTs, driven by albuminuria outcomes: dulaglutide, liraglutide, semaglutide (SQ)	• See labels for renal dose considerations of individual agents • No dose adjustment for dulaglutide, liraglutide, semaglutide • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ; oral (semaglutide)	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined (liraglutide, dulaglutide, exenatide extended release, semaglutide) • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected
GIP and GLP-1 RA	Very high	No	Loss (very high)	Under investigation	Under investigation	Under investigation	• See labels for renal dose considerations • No dose adjustment • Monitor renal function when initiating or escalating doses in patients with renal impairment reporting severe adverse GI reactions	SQ	High	• Risk of thyroid C-cell tumors in rodents; human relevance not determined • Counsel patients on potential for GI side effects and their typically temporary nature; provide guidance on dietary modifications to mitigate GI side effects (reduction in meal size, mindful eating practices [e.g., stop eating once full], decreasing intake of high-fat or spicy food); consider slower dose titration for patients experiencing GI challenges • Pancreatitis has been reported in clinical trials but causality has not been established. Discontinue if pancreatitis is suspected • Evaluate for gallbladder disease if cholelithiasis or cholecystitis is suspected

Pharmacologic Approaches to Glycemic Management: Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S140-S157

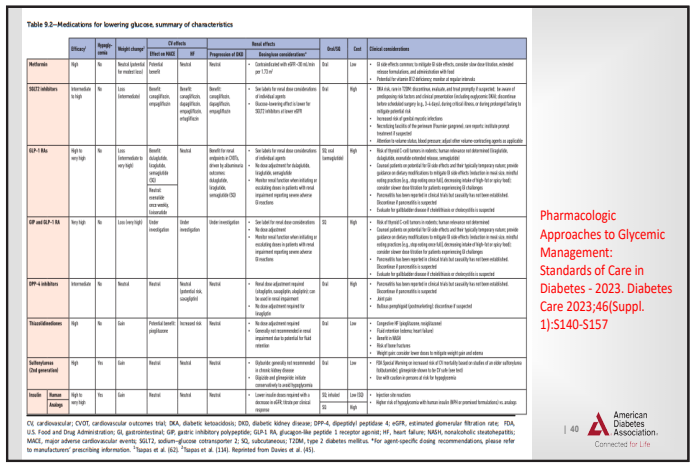
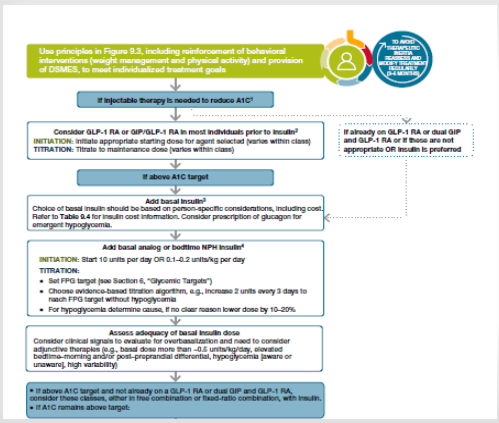


Table 9.2—Medications for lowering glucose, summary of characteristics

Pharmacologic Approaches to Glycemic Management: Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S140-S157

PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT



Pharmacologic Approaches to Glycemic Management: *Standards of Care in Diabetes - 2023. Diabetes Care* 2023;46(Suppl. 1):S140-S157

Tirzepatide – Mounjaro by Lilly

- **May 13, 2022, the U.S. Food and Drug Administration approved Mounjaro (tirzepatide) injection, a first-in-class medicine that activates both the GLP-1 and GIP receptors**, which leads to improved blood sugar control. Tirzepatide is **administered by sub-Q injection skin once weekly**, with the dose adjusted as tolerated to meet blood sugar goals. It is indicated to improve blood sugar control in adults with type 2 diabetes, as an addition to diet and exercise. Tirzepatide was effective at improving blood sugar and was more effective than the other diabetes therapies with which it was compared in clinical studies.
- **Three different doses of terzepatide (5 milligrams, 10 milligrams and 15 milligrams) were evaluated in five clinical trials as either a stand-alone therapy or as an add-on to other diabetes medicines.** The efficacy of Mounjaro was **compared to placebo, a GLP-1 receptor agonist (semaglutide) and two long-acting insulin analogs.**
  - https://www.fda.gov/news-events/press-announcements/fda-approves-novel-dual-targeted-treatment-type-2-diabetes

Tirzepatide – Mounjaro

- **Tirzepatide enhances first- and second-phase insulin secretion, and reduces glucagon levels, both in a glucose dependent manner.**
  - **Tirzepatide reduces fasting and postprandial glucagon concentrations. Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo after 28 weeks of treatment.**
  - **Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time.**
  - **Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.**
  - **Elimination half-life of approximately 5 days**

Table 4: Results at Week 40 in a Trial of MOUNJARO versus Semaglutide 1 mg in Adult Patients with Type 2 Diabetes Mellitus Added to Metformin

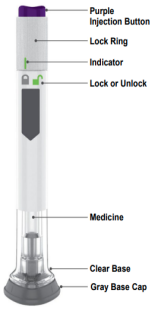
SURPASS 2 Trial

	Semaglutide 1 mg	MOUNJARO 5 mg	MOUNJARO 10 mg	MOUNJARO 15 mg
Modified Intent-to-Treat (mITT) Population (N)[a]	468	470	469	469
HbA1c (%)				
Baseline (mean)	8.3	8.3	8.3	8.3
Change at Week 40[b]	-1.9	-2.0	-2.2	-2.3
Difference from semaglutide[b] (95% CI)	--	-0.2[c] (-0.3, -0.0)	-0.4[d] (-0.5, -0.3)	-0.5[d] (-0.6, -0.3)
Patients (%) achieving HbA1c <7%[e]	79	82	86[f]	86[f]
Fasting Serum Glucose (mg/dL)				
Baseline (mean)	171	174	174	172
Change at Week 40[b]	-49	-55	-59	-60
Body Weight (kg)				
Baseline (mean)	93.7	92.5	94.8	93.8
Change at Week 40[b]	-5.7	-7.6	-9.3	-11.2
Difference from semaglutide[b] (95% CI)	--	-1.9[c] (-2.8, -1.0)	-3.6[d] (-4.5, -2.7)	-5.5[d] (-6.4, -4.6)

Tirzepatide – Mounjaro

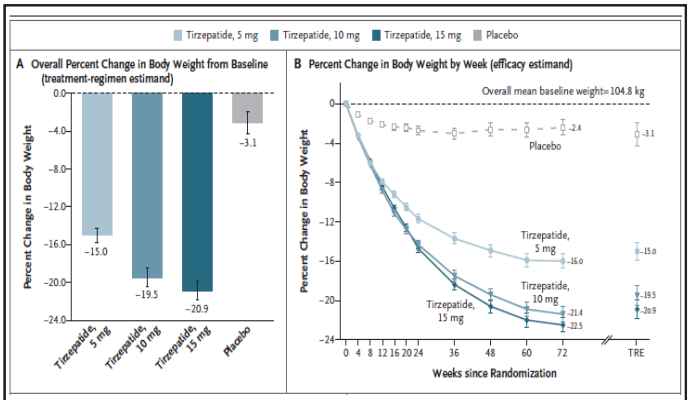
Available in **boxes of 4 single dose pens (titration 4 weeks at each dose)**

- 2.5 mg/0.5 mL single-dose pen
- 5 mg/0.5 mL single-dose pen
- 7.5 mg/0.5 mL single-dose pen
- 10 mg/0.5 mL single-dose pen
- 12.5 mg/0.5 mL single-dose pen
- 15 mg/0.5 mL single-dose pen
- **Cost: list price of $974.33 for four weekly doses regardless of dose size, a cost that adds up to about $12,666 per year**
- Store your Pen in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not freeze!
- You may store your Pen at room temperature up to 86°F (30°C) for up to 21 days and protect from light.



SURMOUNT-1 Trial : Tirzepatide Once Weekly for the Treatment of Obesity (NOT FDA Approved)

- A phase 3 double-blind, randomized, controlled trial, in **2539 adults with a body-mass index (BMI of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes**, in a 1:1:1:1 ratio to receive once-weekly, subcutaneous **tirzepatide (5 mg, 10 mg, or 15 mg) or placebo for 72 weeks, including a 20-week dose-escalation period.**
- **Coprimary end points were the percentage change in weight from baseline and a weight reduction of 5% or more.**
  - June 4, 2022, at NEJM.org. DOI: 10.1056/NEJMoa2206038



– June 4, 2022, at NEJM.org. DOI: 10.1056/NEJMoa2206038

Tirzepatide – Mounjaro

- **10/6/2022 Lilly announced that the FDA granted tirzepatide a "fast track" review to be designated as a treatment for obesity.** To receive this label, **Lilly will be using data from the SURMOUNT-1 trial and the ongoing SURMOUNT-2 trial, which is investigating tirzepatide in people with type 2 diabetes who have excess weight or obesity.**
- Although **the SURMOUNT-2 trial will not be completed until April 2023, the FDA's fast-track designation allows for rolling submission of trial data.** This means the FDA can review data as it comes in, instead of waiting for the entire trial to conclude first. This expedites the review process, resulting in a potentially sooner approval date.

Bexagliflozin – Brenzavvy by TheracosBio

- **January 20, 2023 –the FDA approved Brenzavvy™ (bexagliflozin), the 5th oral sodium-glucose cotransporter 2 (SGLT2) inhibitor** indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.
- **Recommended dose: 20 mg once daily, taken in the morning, with or without food. Do not crush or chew the tablet.**
- Assess renal function before initiating bexagliflozin and as clinically indicated. Correct volume depletion before initiating.
- **Not recommended if eGFR less than 30 mL/min/1.73 m2.**
- **Cost: 20 mg tabs**

Bexagliflozin – Brenzavvy

Clinical Trial Data:

- 207 adults with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) by diet and exercise. **Monotherapy with bexagliflozin for 24 weeks reduced A1c by ~ 0.4% more than placebo and FBS by 16mg%.**
- 317 adults with type 2 diabetes mellitus inadequately controlled (HbA1c between 7.5% and 10.5%) by metformin monotherapy (≥ 1,000 mg/day or ≥ 1,500 mg/day for ≥ 8 weeks depending on country) participated in a randomized, double-blind, multi-center, 24-week, placebo-controlled trial. **Bexagliflozin added to metformin reduced A1c by ~0.5% more than placebo and FBS by 22 mg%.**
- 426 adults with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) by metformin monotherapy participated in a randomized, double-blind, multi-center, 60-week, active comparator-controlled trial with bexagliflozin versus glimepiride as add on therapy with metformin. **Bexagliflozin and glimepiride had similar effects on A1c and only difference of 8mg% in FBS and 4 Kg weight loss in favor of bexagliflozin.**

Bexagliflozin – Brenzavvy

- 384 adults with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 11%) by metformin monotherapy participated in a randomized, double-blind, multi-center, 24-week, active comparator-controlled trial with bexagliflozin vs. sitagliptin as add on therapy. **Sitagliptin reduced A1c 0.1% more than bexagliflozin and FBS by 5 mg% less.**
- 312 adults with inadequately controlled type 2 diabetes mellitus (HbA1c between 7.0% and 10.5%) and **moderate renal impairment (eGFR between 30 and 60 mL/min/1.73 m2)** participated in a randomized, double-blind, multi-center, 24-week, placebo-controlled trial. **Bexaglifozin reduced Ac 0.3% more than placebo and FBS by 14 mg%,**

Bexagliflozin – Brenzavvy

- **The BEST Trial - 1,701 adults with inadequately controlled type 2 diabetes mellitus (HbA1c between 7% and 11%) who had either established CVD (including a history of atherosclerotic vascular disease or a history of heart failure) or multiple risk factors for CVD (no restrictions on background antihyperglycemic medication use, aside from treatment with an SGLT2 inhibitor,** (99.4%) were treated with one or more antidiabetic medications including metformin (77%), insulin (53%), sulfonylureas (40%), DPP-4 inhibitors (13%) and thiazolidinediones (3%)). **Bexagliflozin reduced A1c by ~0.4% and FBS ~ 20 mg% more than placebo.**
- **Major Adverse Cardiovascular Events (4-point MACE) (a composite of cardiovascular death, non-fatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina). The minimum treatment duration was 52 weeks (median duration 2.4 years).** In this trial, the proportion of patients who experienced **at least one MACE event was 10.1% (57/567) in the placebo group and 7.9% (89/1132) in the bexagliflozin group** (4.2 MACE events per 100 person-years for placebo and 3.3 MACE events per 100 person-years for bexagliflozin). [estimated **hazard ratio of 0.77 (95% CI: 0.56, 1.08)]. Bexagliflozin was not superior to the placebo in reducing MACE.**

Bexagliflozin – Brenzavvy

WARNINGS AND PRECAUTIONS:

- Ketoacidosis
- Lower limb amputation
- Volume depletion
- Urosepsis and pyelonephritis
- Hypoglycemia
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Genital mycotic infection

Bexagliflozin – Brenzavvy

Lower Limb Amputation

- **An increased incidence of lower limb amputations occurred in Bexagliflozin treated patients compared to placebo-treated patients (8.3 versus 5.1 events per 1,000 patient-years) in a randomized, placebo-controlled trial evaluating patients with type 2 diabetes** who had either established cardiovascular disease (CVD) or were at risk for CVD.
- **Of the 23 bexagliflozin-treated patients who had amputations, 15 were amputations of the toe and midfoot and 8 were amputations above and below the knee. Some patients had multiple amputations.**
- **Lower limb infections, gangrene, ischemia, and osteomyelitis were the most common precipitating medical events leading to the need for an amputation.** The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

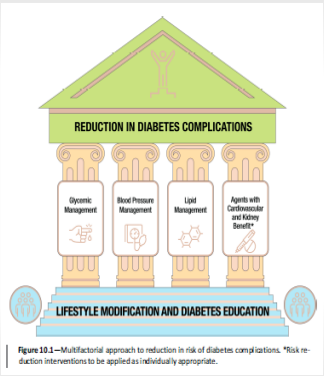
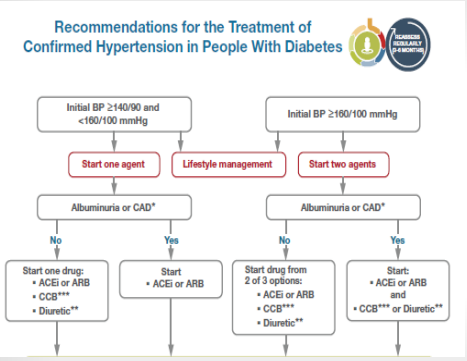


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

Cardiovascular Disease and Risk Management:
Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S158-S190

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT

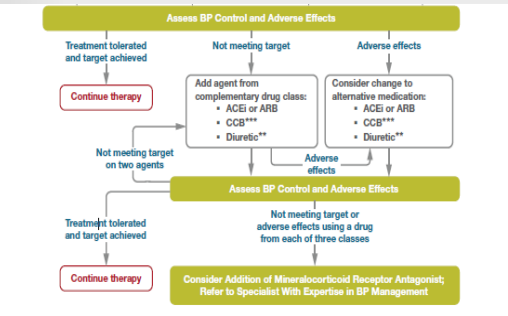


Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes (1 of 2)

Figure 10.2—Recommendations for the treatment of confirmed hypertension in people with diabetes. *An ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) is suggested to treat hypertension for people with coronary artery disease (CAD) or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for individuals with urine albumin-to-creatinine ratio >/=300 mg/g creatinine. **Thiazide-like diuretic; long-acting agents shown to reduce cardiovascular events, such as chlorthalidone and indapamide, are preferred. ***Dihydropyridine calcium channel blocker (CCB). BP, blood pressure. Adapted from de Boer et al. (20).

Cardiovascular Disease and Risk Management:
Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S158-S190

CARDIOVASCULAR DISEASE AND RISK MANAGEMENT



Recommendations for the Treatment of Confirmed Hypertension in People with Diabetes (2 of 2)

Cardiovascular Disease and Risk Management:
Standards of Care in Diabetes - 2023. Diabetes Care 2023;46(Suppl. 1):S158-S190

CHRONIC KIDNEY DISEASE AND RISK MANAGEMENT

Chronic Kidney Disease—Treatment

11.2 **Optimize glucose control to reduce the risk or slow the progression of chronic kidney disease. A**

11.3 **Optimize blood pressure control and reduce blood pressure variability to reduce the risk or slow the progression of chronic kidney disease. A**

11.4a In **nonpregnant people with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with moderately increased albuminuria (urinary albumin-to-creatinine ratio 30– 299 mg/g creatinine) B** and is strongly recommended for those with severely increased albuminuria **(urinary albumin-to-creatinine ratio ≥300 mg/g creatinine) and/or estimated glomerular filtration rate <60 mL/min/1.73 m2. A**

CHRONIC KIDNEY DISEASE AND RISK MANAGEMENT

Chronic Kidney Disease—Treatment (continued)

11.4b Periodically monitor serum creatinine and potassium levels for the development of increased creatinine and hyperkalemia when ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists are used, or hypokalemia when diuretics are used. B

11.4c **An ACE inhibitor or an angiotensin receptor blocker is not recommended for the primary prevention of chronic kidney disease in people with diabetes who have normal blood pressure, normal urinary albumin-to-creatinine ratio (<30 mg/g creatinine), and normal estimated glomerular filtration rate. A**

CHRONIC KIDNEY DISEASE AND RISK MANAGEMENT

Chronic Kidney Disease—Treatment (continued)

11.4d **Do not discontinue renin-angiotensin system blockade for increases in serum creatinine (≤30%) in the absence of volume depletion. A**

11.5a For **people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m2 and urinary albumin ≥200 mg/g creatinine. A**

CHRONIC KIDNEY DISEASE AND RISK MANAGEMENT

Chronic Kidney Disease—Treatment (continued)

11.5b For people with type 2 diabetes and diabetic kidney disease, use of a sodium–glucose cotransporter 2 inhibitor is recommended to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated glomerular filtration rate ≥20 mL/min/1.73 m2 and urinary albumin ranging from normal to 200 mg/g creatinine. B

11.5c In **people with type 2 diabetes and diabetic kidney disease, consider use of sodium–glucose cotransporter 2 inhibitors (if estimated glomerular filtration rate is ≥20 mL/min/1.73 m2), a glucagon-like peptide 1 agonist, or a nonsteroidal mineralocorticoid receptor antagonist (if estimated glomerular filtration rate is ≥25 mL/min/1.73 m2) additionally for cardiovascular risk reduction .** A

 American Diabetes Association. Connected for Life

FDA Approved SGLT-2 Inhibitors for CKD

- **Dapagliflozin: To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. (DAPA-CKD)**
  - Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m2
- **Canagliflozin: To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria. (CREDENCE)**
  - Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m2
- **Empagliflozin: Pending FDA approval based upon data from EMPA-KIDNEY in adult CKD patients with and without type 2 diabetes.**
  - Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m2

EMPA-KIDNEY design

Population: a broad range of patients with chronic kidney disease at risk of progression (eGFR 20-44; or 45-90 mL/min/1.73 m^2 with UACR ≥200 mg/g) in 8 countries

Intervention

Investigator-judged clinically appropriate RAS blockade, where indicated & tolerated

- Empagliflozin 10 mg once daily
- Placebo once daily

Primary composite outcome

CV death OR Kidney disease progression

- End-stage kidney disease; Renal death
- eGFR change ≥40% eGFR decline, or to <10 mL/min/1.73m^2

Key secondary outcomes

- All hospitalizations (recurrent events)
- All-cause death
- CV death or HF hospitalization

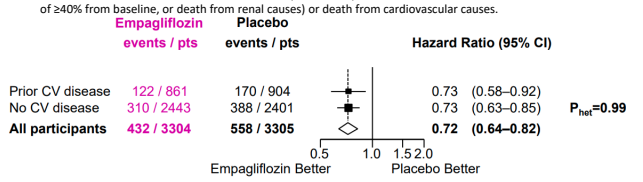
EMPA-KIDNEY Collaborative Group, *Nephrol Dial Transplant.* 2022;37:1317-29

MRC Population Health Research Unit

1

Primary outcome: by prior CV disease

The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m2 , a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.



- Average follow up: 2 years
- 128 CV deaths occurred

MRC Population Health Research Unit

EMPA-KIDNEY

3

Recurrent events analyses: CV outcomes

Outcome	Analysis	Empagliflozin	Placebo	HR (95% CI)
HF hospitalization	First event	88	107	0.80 (0.60-1.06)
	Total events	118	154	0.78 (0.59-1.05)
CV death or HF hospitalization	First event	131	152	0.84 (0.67-1.07)
	Total events	166	210	0.83 (0.64-1.07)
MACE*	First event	200	213	0.93 (0.76-1.12)
	Total events	251	290	0.90 (0.72-1.12)

*MACE: CV death, MI, stroke or HF hospitalization

MRC Population Health Research Unit

EMPA-KIDNEY

4

SGLT2 Inhibitor Therapy for High-Risk Patients:
EMPA-KIDNEY trial and Meta-Analysis of Major Trials of SGLT2 Inhibitor Therapy

Purpose:

EMPA-KIDNEY

- Effects of SGLT2i empagliflozin on CVD, progressions of kidney disease and need for hospitalization with CKD.

Meta-Analysis of 13 SGLT2i Trials

- Effect of SGLT2i on CV and other outcomes in high-risk groups.

Design:

EMPA-KIDNEY

- Randomized trial N= 6609 (8 countries), with CKD comparing SGLT2i empagliflozin vs placebo.

Meta-analysis of 13 SGLT2i Trials

- Data analysis of 13 SGLT2i trials involving 90,000 participants with Type 2 Diabetes and with or at risk for CVD, HF, CKD.

RESULTS

EMPA-KIDNEY –empagliflozin vs. placebo

Reduced progression of kidney disease or cardiovascular death by 28%
- Consistent benefit in those with or without cardiovascular disease

Reduced the need for hospitalization by 14%
- Rates of hospitalization were very high
- Consistent benefit in those with or without cardiovascular disease

Cardiovascular outcomes: Non-significant reductions observed in:
- Heart failure hospitalization
- Cardiovascular death or heart failure hospitalization
- Major cardiovascular events

Meta-Analysis of Major Trials of SGLT2 Inhibitor Therapy

	SGLT2i events/participants	Placebo events/participants	RR (95% CI)
CV Death or Hospitalization for HF (totals)			
Diabetes	3056/40691	3233/34113	0.77 (0.73, 0.81)
No diabetes	760/7792	943/7813	0.79 (0.72,0.87)
CV Death (totals) 14% reduction in CV Death			
Diabetes	1908/40691	17743/341113	0.86 (0.80,0.92)
No diabetes	422/7792	477/7813	0.88 (0.78, 1.01)

Meta-Analysis Results:
- With type 2 diabetes: reductions in (i) cardiovascular death (ii) cardiovascular death + heart failure hospitalization in all groups of high-risk participants
- Without type 2 diabetes reductions in (i) cardiovascular death (ii) cardiovascular death + heart failure hospitalization in participants with heart failure; but less information in patients with chronic kidney disease.

Presented by: **David Preiss**, PhD, Medical Research Council Population Health Research Unit, University of Oxford, UK Scientific Sessions 2022. © 2022, American Heart Association. All rights reserved

Results reflect the data available prior to the time of presentation.

Scientific Sessions #AHA22

CHRONIC KIDNEY DISEASE AND RISK MANAGEMENT

Chronic Kidney Disease—Treatment (continued)

11.5d In **people with chronic kidney disease and albuminuria who are at increased risk for cardiovascular events or chronic kidney disease progression, a nonsteroidal mineralocorticoid receptor antagonist shown to be effective in clinical trials is recommended to reduce chronic kidney disease progression and cardiovascular events.** A

11.6 In people with chronic kidney disease who have ≥300 mg/g urinary albumin, a reduction of 30% or greater in mg/g urinary albumin is recommended to slow chronic kidney disease progression. B

American Diabetes Association. Connected for Life

Finerenone – Kerendia by Bayer

- **July 9, 2021, FDA Priority Review Approval - Finerenone a non-steroidal mineralocorticoid receptor antagonist (MRA) indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes.**
- The terminal half-life of finerenone is approximately 2 to 3 hours. Finerenone is primarily metabolized by CYP3A4 (90%) and to a lesser extent by CYP2C8 (10%) to inactive metabolites.

Finerenone – Kerendia

- **Finerenone is a nonsteroidal, dihydropyridine-based mineralocorticoid receptor antagonist with high mineralocorticoid receptor selectivity and potency**. The **mineralocorticoid receptor is expressed** in epithelial (eg, **kidney**) and nonepithelial (eg, **heart, vascular) tissues and is activated by aldosterone and cortisol**. Functions of the mineralocorticoid receptor include **mediation of renal sodium reabsorption and potassium excretion** and regulation of gene transcription. Finerenone blocks mineralocorticoid receptor–mediated sodium reabsorption and also mineralocorticoid receptor overactivation; **mineralocorticoid receptor overactivation in renal epithelial cells and cardiac myocytes increases expression of proinflammatory and fibrotic proteins and is thought to contribute to the pathogenesis of cardiac and renal fibrosis and inflammation.** Finerenone has no relevant affinity for androgen, progesterone, estrogen, or glucocorticoid receptors.

Finerenone – Kerendia

- **DRUG INTERACTIONS: Finerenone is a CYP3A4 substrate; coadministration with a strong CYP3A4 inhibitor (itraconazole) increased finerenone exposure by more than 400%.** Concomitant use of **finerenone with strong CYP3A4 inhibitors is contraindicated, and concomitant intake of grapefruit or grapefruit juice is not recommended.**
- **Coadministration with a moderate CYP3A4 inhibitor (erythromycin) increased finerenone mean AUC and Cmax by 248% and 88%, respectively, while coadministration with a weak CYP3A4 inhibitor (amiodarone) increased finerenone AUC by 21%.** Concomitant use of finerenone with a moderate or weak CYP3A4 inhibitor **may increase the risk of adverse reactions.** If concomitant use is necessary**, monitor serum potassium during therapy initiation or dosage adjustment** of either finerenone or the moderate or weak CYP3A4 inhibitor, and adjust finerenone dosage as appropriate.

Finerenone – Kerendia

- **FIDELIO-DKD trial – Finerenone vs. placebo in 5,674 adults** (18 years or older) meeting diagnostic criteria for **type 2 diabetes and CKD**, defined as either persistent moderately elevated albuminuria (30 to less than 300 mg/g) and eGFR 25 to less than 60 mL/minute/1.73 m2 and documented diabetic retinopathy or persistent severely elevated albuminuria (300 to 5,000 mg/g) and eGFR 25 to less than 75 mL/minute/1.73 m2.
- Patients were **required to have received treatment with an ACE inhibitor or ARB at the maximally tolerated labeled dose for 4 weeks or more** and have a serum **potassium level of 4.8 mEq/L or less at screening**.
  - Exclusion criteria included significant nondiabetic kidney disease; hemoglobin A1C (HbA1C) greater than 12%; uncontrolled arterial hypertension; systolic blood pressure less than 90 mm Hg; clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (NYHA class II to IV); transient ischemic cerebral attack, stroke, acute coronary syndrome (ACS), or hospitalization for worsening heart failure in the 30 days prior to screening; Addison disease; Child-Pugh class C hepatic insufficiency; concomitant therapy with eplerenone, spironolactone, a renin inhibitor, or a potassium-sparing diuretic that could not be discontinued at least 4 weeks prior to screening;
    - N Engl J Med 2020;383:2219-29

Finerenone – Kerendia

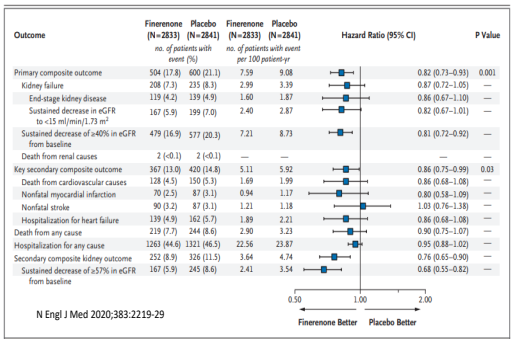
Primary End Point(s) at a mean of 2.6 years:

- **Composite of kidney failure, sustained decrease in eGFR of 40% or more from baseline** over a period of at least 4 weeks, **or death from renal causes** occurred in **17.8% of the finerenone group and 21.1% of the placebo group; hazard ratio (HR) was 0.82** (95% CI, 0.73 to 0.93; P=0.001). **NNT=31**
- Kidney failure occurred in 7.3% and 8.3% of patients in the finerenone and placebo groups, respectively, and sustained decrease in eGFR of 40% or greater from baseline occurred in 16.9% and 20.3%, respectively; death from renal causes occurred in less than 0.1% in both groups.

Secondary End Point(s):

- **Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure occurred in 13% of the finerenone group and 14.8% of the placebo group; HR was 0.86** (95% CI, 0.75 to 0.99; P=0.03) **NNT=56.**
  - N Engl J Med 2020;383:2219-29

Finerenone – Kerendia



Outcome	Finerenone (N=2833) no. of patients with event (%)	Placebo (N=2841)	Finerenone (N=2833) no. of patients with event per 100 patient-yr	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m²	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—

N Engl J Med 2020;383:2219-29

Finerenone – Kerendia

Table 2. Adverse Reactions With Finerenone (Incidence ≥1% and Greater Than With Placebo) in the FIDELIO-DKD Trial(Bakris 2020, Kerendia July 2021)

Adverse reactions	Finerenone (n=2,827)	Placebo (n=2,831)
Hyperkalemia	15.8% (18.3%[a])	7.8% (9%[a])
Anemia	7.4%	6.7%
eGFR decreased	6.3%	4.7%
Hypotension	4.8%[a]	3.4%[a]
Hospitalization due to acute kidney injury	1.9%	1.7%
Serious hyperkalemia	1.6%	0.4%
Hyponatremia	1.4%[a]	0.7%[a]
Hospitalization due to hyperkalemia	1.4%	0.3%
[a] Value from finerenone prescribing information		

Initiation of finerenone may cause a small decrease in eGFR that occurs within the first 4 weeks of starting therapy and then stabilizes. In FIDELIO-DKD, this decrease was reversible after treatment discontinuation. (Kerendia July 2021)

Finerenone – Kerendia

DOSING: The recommended starting finerenone dose is based on baseline eGFR; see Table 3 for a summary of recommended starting doses. The target daily dose is 20 mg. (Kerendia 2021)

Table 3. Recommended Starting Dose of Finerenone Based on eGFR (Kerendia July 2021)

Baseline eGFR	Starting finerenone dose
≥60 mL/minute/1.73 m²	20 mg once daily
25 to <60 mL/minute/1.73 m²	10 mg once daily
<25 mL/minute/1.73 m²	Not recommended

Finerenone can be taken without regard to food. The tablets may be crushed and mixed with water or soft foods immediately prior to oral administration. If a dose is missed, it should be taken as soon as possible,

Table 4. Recommended Finerenone Dose Adjustments Based on Serum Potassium and Current Finerenone Dose (Kerendia July 2021)

Serum potassium (mEq/L)	Current finerenone dose: 10 mg once daily	Current finerenone dose: 20 mg once daily
≤4.8 mEq/L	Increase dose to 20 mg once daily.[a]	Maintain 20 mg once daily.
>4.8 to 5.5 mEq/L	Maintain 10 mg once daily.	Maintain 20 mg once daily.
>5.5 mEq/L	Withhold finerenone. Consider restarting at 10 mg once daily when serum potassium ≤5 mEq/L.	Withhold finerenone. Restart at 10 mg once daily when serum potassium ≤5 mEq/L.
[a] If eGFR has decreased >30% from previous measurement, maintain 10 mg dose.		

Finerenone – Kerendia

- **Tablets: 10 mg and 20 mg once a day with or without food.**
- **Cost for both strengths is ~ $650.00 for 30 tablets**
- **Should we now consider triple therapy for our patients with diabetes and CKD? (ACEI or ARB plus an SGLT-2 inhibitor and now finereone)**
  - **We have good data with an ACEI or ARB plus an SGLT-2 inhibitor and also with an ACEI or ARB plus finereone but only very limited data with all three. (4.6% of pts in FIDELIO-DKD trial were also taking an SGLT-2 inhibitor and they did appear to have a lower risk of hyperkalemia? We need more data!**

Teplizumab-mzwv injection – Tzield

by Provention Bio

- **November 17, 2022, the U.S. Food and Drug Administration approved Tzield (teplizumab-mzwv) injection to delay the onset of stage 3 type 1 diabetes in adults and pediatric patients 8 years and older who currently have stage 2 type 1 diabetes.**
  - **Priority Review and Breakthrough Therapy designations for this indication.**
- Last year, the **FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 10-7 in favor of teplizumab to delay clinical type 1 diabetes mellit**us. The **question before the committee was whether or not the benefits of teplizumab, anti-CD3 monoclonal antibody, outweigh the risks.**
- While the committee ultimately supported the question in the affirmative, there were **concerns raised by members, specifically around the small size of the study, safety and efficacy data. Many wanted a confirmatory trial in an expanded patient population.**

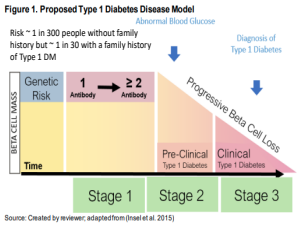
Teplizumab-mzwv injection – Tzield

- **"More specifically, committee members stressed that they couldn't fully grasp the long-term malignancies, the risk of diabetic ketoacidosis (DKA) and three deaths documented in the study," (FDA did not believe the deaths were related to the study medication).**
- Mechanism of Action: Teplizumab is a **humanized monoclonal antibody that targets the cluster of differentiation 3 (CD3) antigen, which is co-expressed with the T-cell receptor (TCR) on the surface of T lymphocytes.** Though the mechanism of action of teplizumab for the proposed indication has not been confirmed, it appears to involve weak agonistic activity on signaling via the TCR-CD3 complex, which is **thought to expand regulatory T-cells and re-establish immune tolerance.**

ADA Statement to the FDA on Teplizumab

- "To provide an individual a 2-year delay from the symptoms, sequalae, and burden of T1D is clinically meaningful, as there will likely be long-term benefits for glycemic control and the reduction in – or delayed, or decreased severity of – acute and long-term complications. Additionally, the quality of life significantly improves, not only for the person living with T1D, but also for their family. The 2-year delay in symptom onset also reduces the stress on young developing bodies and reduces the burden on the healthcare system."
- **"Given the urgent need for a monoclonal antibody that modulates the response of the T-lymphocytes that mediate the destruction of the insulin-producing beta cells in the islets of the pancreas, ADA, on behalf of individuals living with T1D urges the FDA to promptly review and give serious consideration to rapid approval to this clinically meaningful treatment."**
  - May 26, 2021 Robert Gabbay, MD, PhD, Chief Scientific & Medical Officer American Diabetes Assoc.

Teplizumab-mzwv injection – Tzield



Stage 1 genetic risk, autoantibodies, normal glucose
Stage 2 genetic risk, 2 or more autoantibodies and elevated glucose with glucose loads but below diagnostic threshold

- Teplizumab binds to certain immune system cells and delays progression to stage 3 type 1 diabetes. **Teplizumab may deactivate the immune cells that attack insulin-producing cells, while increasing the proportion of cells that help moderate the immune response.** It is administered by intravenous infusion once daily for 14 consecutive days in **adults and pediatric patients 8 years and older who currently have stage 2 type 1 diabetes.**

Teplizumab-mzwv injection – Tzield

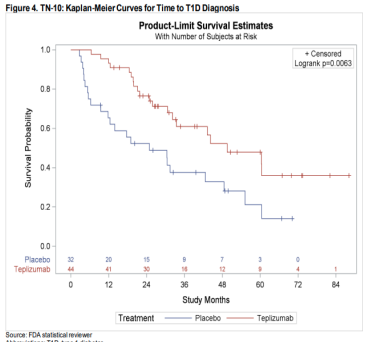
- **TN-10 Study** - A **phase 2, randomized, placebo-controlled, double-blind trial of teplizumab** (an Fc receptor–nonbinding anti-CD3 monoclonal antibody) **involving relatives of patients with type 1 diabetes who did not have diabetes but were at high risk for development of clinical disease.** Patients were randomly assigned to a single 14-day course of teplizumab or placebo, and follow-up for progression to clinical type 1 diabetes was performed with the use of oral glucose-tolerance tests at 6-month intervals.
- A **total of 76 participants (55 [72%] of whom were ≤18 years of age) underwent randomization** — 44 to the teplizumab group and 32 to the placebo group. The **median time to the diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group;** the disease was diagnosed in 19 (43%) of the participants who received teplizumab and in 23 (72%) of those who received placebo. The **hazard ratio for the diagnosis of type 1 diabetes (teplizumab vs. placebo) was 0.41** (95% confidence interval, 0.22 to 0.78; P=0.006 by adjusted Cox proportional-hazards model). The **annualized rates of diagnosis of diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group.** N Engl J Med 2019; 381:603-613

Teplizumab-mzwv injection – Tzield

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Teplizumab (N=44)	Placebo (N=32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro-insulin	20 (45)	11 (34)
Anti–IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)

* Percentages may not total 100 because of rounding. GAD65 denotes glutamic acid decarboxylase 65, IA-2 islet antigen 2, ICA islet-cell autoantibody, IQR interquartile range, and ZnT8 zinc transporter 8.
† Participants in this category may have had more than one sibling with type 1 diabetes.
‡ Shown are the autoantibodies for which participants were positive at the time of randomization. All participants were positive for at least two autoantibodies before randomization.



N Engl J Med 2019; 381:603-613

Teplizumab-mzwv injection – Tzield

Table 1. Common Adverse Reactions[1] in Adult and Pediatric Patients Aged 8 Years and Older with Stage 2 Type 1 Diabetes (Study TN-10)[2]

Adverse Reaction	Placebo N=32	TZIELD N=44
Lymphopenia	6%	73%
Rash[3]	0%	36%
Leukopenia	0%	21%
Headache	6%	11%
Neutropenia	3%	5%
Increased alanine aminotransferase	3%	5%
Nausea	3%	5%
Diarrhea	0%	5%
Nasopharyngitis	0%	5%

[1] That occurred during treatment and through 28 days after the last study drug administration
[2] Adverse reactions that occurred in 2 or more TZIELD-treated patients
[3] Composite of rash-related terms including rash erythematous, rash macular, rash papular, rash maculo-papular, rash pruritic

Monitor liver enzymes during treatment. Discontinue treatment in patients who develop elevated ALT or AST more than 5 times the upper limit of normal (ULN) or bilirubin more than 3 times ULN.
Monitor white blood cell counts during the treatment period. If prolonged severe lymphopenia (<500 cells per mcL lasting 1 week or longer) develops, discontinue treatment.

- **Cytokine release syndrome (CRS)** has been observed in TZIELD-treated patients. In clinical trials, CRS was **reported in 5% of treated patients compared to 0.8% of control-treated patients during the treatment period and through 28 days** after the last study drug administration.
- **CRS manifestations** in treated patients **included fever, nausea, fatigue, headache, myalgia, arthralgia, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), and increased total bilirubin. These manifestations typically occurred during the first 5 days of treatment.**

N Engl J Med 2019; 381:603-613

Teplizumab-mzwv injection – Tzield

- Severe Infections - Bacterial and viral infections have occurred in teplizumab-treated patients. In clinical trials, **teplizumab-treated patients had a higher rate of serious infections (3.5%) than control-treated patients (2%), including gastroenteritis, cellulitis, pneumonia, abscess, and sepsis.**
- Vaccinations - **Teplizumab may interfere with the immune response to vaccination and decrease vaccine efficacy.**
  - **Administer all age-appropriate vaccinations prior to starting teplizumab.**
  - **Inactivated or mRNA vaccinations are not recommended within the 2 weeks prior to treatment, during treatment, or 6 weeks after completion of treatment.**
  - **Live-attenuated vaccinations are not recommended within the 8 weeks prior to treatment, during treatment, or up to 52 weeks after treatment.**

Teplizumab-mzwv injection – Tzield

- **Recommended Dosage:**
  - Injection: 2 mg per 2 mL (1 mg/mL) clear and colorless solution in a single-dose vial.
  - Administer by **intravenous infusion (over a minimum of 30 minutes), using a body surface area-based dosing, once daily for 14 consecutive days as follows:**
    - **Day 1: 65 mcg/m2**
    - **Day 2: 125 mcg/m2**
    - **Day 3: 250 mcg/m2**
    - **Day 4: 500 mcg/m2**
    - **Days 5 through 14: 1,030 mcg/m2**
  - Do not administer two doses on the same day.
- **Premedicate prior to infusion for the first 5 days of dosing with: (1) a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen, (2) an antihistamine, and/or (3) an antiemetic.**
- Treat symptoms of CRS with antipyretics, antihistamines and/or antiemetics. If severe CRS develops, consider temporarily pausing dosing for 1-2 days (and administer the remaining doses to complete the full 14-day course on consecutive days) or discontinuing treatment.
  - **Cost: $13,850/vial or $194,000 per 14 days**

Teplizumab-mzwv injection – Tzield

- Issues that we need to address?
- If we are going to consider using it, do you allow non-endocrinologists to prescribe it as it may not be reasonable to wait until and endocrinologist can see the patient?
- Can we make it easy to complete the 14 consecutive days for the infusions and provide a convenient time from work and school for the two weeks?
- Insurance coverage and screening for eligible patients?
  - You qualify for free screening if: you are between the ages of 2.5 and 45, and have a parent, brother/sister or child with T1D OR you are between the ages of 2.5 and 20 and have an aunt/uncle, cousin, grandparent, niece/nephew or half-brother/sister with T1D AND you have not been diagnosed with diabetes.
  - If you have questions, contact TrialNet at 1-800-425-8361 or email info@trialnet.org.

Global Initiative for Asthma (GINA) What's new in GINA 2022?

GINA Global Strategy for Asthma Management and Prevention

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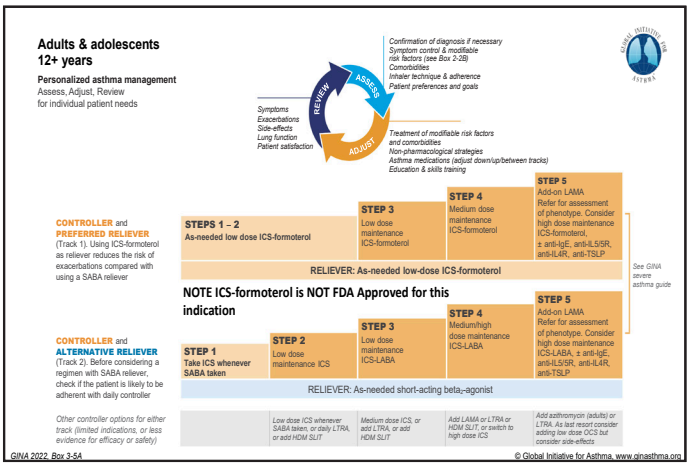
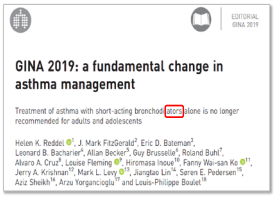


GINA treatment figure for adults and adolescents (≥12 years)

- Treatment options are shown in two tracks
  - This was necessary to clarify how to step treatment up and down with the same reliever
- Track 1, with low dose ICS-formoterol as the reliever, is the preferred strategy
  - Preferred because of the evidence that using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever, with similar symptom control and lung function
- Track 2, with SABA as the reliever, is an 'alternative' (non-preferred) strategy
  - Less effective than Track 1 for reducing severe exacerbations
  - Use Track 2 if Track 1 is not possible; can also consider Track 2 if a patient has good adherence with their controller, and has had no exacerbations in the last 12 months
  - Before considering a regimen with SABA reliever, consider whether the patient is likely to continue to be adherent with daily controller – if not, they will be exposed to the risks of SABA-only treatment
- "Other controller options"
  - These have limited indications, or less evidence for efficacy and/or safety than Track 1 or 2 options
- Step 5
  - A new class of biologic therapy has been added (anti-TSLP)
  - A prompt added about the GINA severe asthma guide

Why not treat with SABA alone?

- Inhaled SABA has been first-line treatment for asthma for 50 years
  - Asthma was thought to be a disease of bronchoconstriction
  - Role of SABA reinforced by rapid relief of symptoms and low cost
- **Regular use of SABA, even for 1–2 weeks, is associated with increased airway hyperresponsiveness , reduced bronchodilator effect, increased allergic response, increased eosinophils** (e.g. Hancox, 2000; Aldridge, 2000)
  - Can lead to a vicious cycle encouraging overuse
  - Over-use of SABA associated with ↑ exacerbations and ↑ mortality (e.g. Suissa 1994, Nwaru 2020)
- Starting treatment with SABA trains the patient to regard it as their primary asthma treatment
- The only previous option was daily ICS even when no symptoms, but adherence is extremely poor
- GINA changed its recommendation once evidence for a safe and effective alternative was available


EDITORIAL
GINA 2019

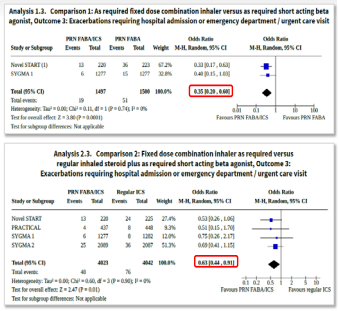
GINA 2019: a fundamental change in asthma management

Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents

Helen K. Reddel, J. Mark FitzGerald, Eric D. Bateman, Leonard B. Bacharier, Allan Becker, Guy Brusselle, Roland Buhl, Alvaro A. Cruz, Louise Fleming, Hiromasa Inoue, Fanny Wai-san Ke, Jerry A. Krishnan, Mark L. Levy, Jiangtao Lin, Søren E. Pedersen, Aziz Sheikh, Arzu Yorgancioglu and Louis-Philippe Boulet

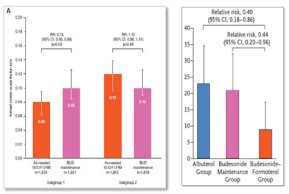
New evidence for as-needed ICS-formoterol in mild asthma

- **Meta-analysis of four all RCTs, n=9,565**
  (Crossingham, Cochrane 2021)
  - 55% reduction in severe exacerbations compared with SABA alone
  - Similar risk of severe exacerbations as with daily ICS + as-needed SABA
  - **ED visits or hospitalizations**
    - **65% lower than with SABA alone**
    - **37% lower than with daily ICS**



New evidence for as-needed ICS-formoterol in mild asthma

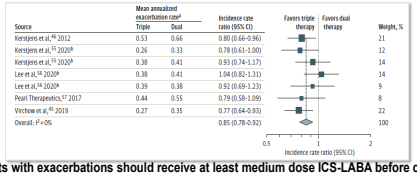
- **Meta-analysis of four all RCTs, n=9,565**
  (Crossingham, Cochrane 2021)
  - **55% reduction in severe exacerbations compared with SABA alone**
  - **Similar risk of severe exacerbations as with daily ICS + as-needed SABA**
  - **ED visits or hospitalizations**
    - **65% lower than with SABA alone**
    - **37% lower than with daily ICS**
- Analysis by previous treatment
  - Patients taking SABA alone had lower risk of severe exacerbations with as-needed ICS-formoterol compared with daily ICS + as-needed SABA *(Bateman, Annals ATS 2021; Beasley, NEJMed 2019)*



Bateman 2021 Beasley 2019

Other changes in medication recommendations for ≥12 years

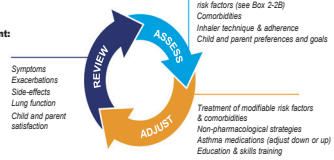
- **Long-acting muscarinic antagonists (LAMA) should not be used as monotherapy for asthma (i.e. without ICS) because of increased risk of severe exacerbations** *(Baan, Pulm Pharmacol Ther 2021)*
- Adding LAMA to ICS-LABA: GRADE review and meta-analysis *(Kim, JAMA 2021)* confirms previous findings
  - Small increase in lung function (mean difference 0.08 L)
  - No clinically important benefits for symptoms or quality of life → don't prescribe for dyspnea
  - Modest overall reduction in exacerbations compared with ICS-LABA (risk ratio 0.83 [0.77, 0.90])



  - **Patients with exacerbations should receive at least medium dose ICS-LABA before considering add-on LAMA**
- Chromone pMDIs (sodium cromoglycate, nedocromil sodium) have been discontinued globally

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

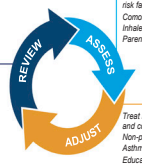
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4R
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*Add-on anti-IL5 or, as last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

*Very low dose: BUD-FORM 100/6 mcg
†Low dose: BUD-FORM 200/6 mcg (metered doses).

Box 3-5B © Global Initiative for Asthma 2022, www.ginasthma.org

Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



Exclude alternative diagnoses
Symptom control & modifiable risk factors
Comorbidities
Inhaler technique & adherence
Parent preferences and goals

Symptoms
Exacerbations
Side-effects
Parent satisfaction

Treat modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE		Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double low dose ICS	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

Box 6-5 © Global Initiative for Asthma 2022, www.ginasthma.org

Patients with features of asthma and COPD

CLINICAL PHENOTYPE - ADULTS WITH CHRONIC RESPIRATORY SYMPTOMS (dyspnea, cough, chest tightness, wheeze)

HIGHLY LIKELY TO BE ASTHMA (if several of the following features) TREAT AS ASTHMA	FEATURES OF BOTH ASTHMA + COPD TREAT AS ASTHMA	LIKELY TO BE COPD (if several of the following features) TREAT AS COPD
HISTORY • Symptoms vary over time and in intensity - Triggers may include laughter, exercise, allergens, seasonal - Onset before age 40 years - Symptoms improve spontaneously or with bronchodilators (minutes) or ICS (days to weeks) • Current asthma diagnosis, or asthma diagnosis in childhood **LUNG FUNCTION** • Variable expiratory airflow limitation • Persistent airflow limitation may be present	**HISTORY** • Symptoms intermittent or episodic - May have started before or after age 40 • May have a history of smoking and/or other toxic exposures, or history of low birth weight or respiratory illness such as tuberculosis • Any of asthma features at left (e.g. common triggers; symptoms improve spontaneously or with bronchodilators or ICS; current asthma diagnosis or asthma diagnosis in childhood) **LUNG FUNCTION** • Persistent expiratory airflow limitation • With or without bronchodilator reversibility	**HISTORY** • Dyspnea persistent (most days) - Onset after age 40 years - Limitation of physical activity - May have been preceded by cough/sputum - Bronchodilator provides only limited relief • History of smoking and/or other toxic exposure, or history of low birth weight or respiratory illness such as tuberculosis • No past or current diagnosis of asthma **LUNG FUNCTION** • Persistent expiratory airflow limitation • With or without bronchodilator reversibility

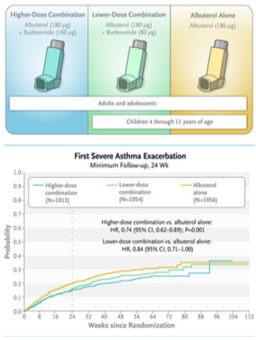
INITIAL PHARMACOLOGICAL TREATMENT (as well as treating comorbidities and risk factors. See Box 3-5A)

• **ICS-CONTAINING TREATMENT IS ESSENTIAL** to reduce risk of severe exacerbations and death. See Box 3-5A - As-needed low dose ICS-formoterol may be used as reliever. See Box 3-5A • **DO NOT GIVE LABA and/or LAMA without ICS** • Avoid maintenance OCS	• **ICS-CONTAINING TREATMENT IS ESSENTIAL** to reduce risk of severe exacerbations and death. See Box 3-5A • Add-on LABA and/or LAMA usually also needed • Additional COPD treatments as per GOLD • **DO NOT GIVE LABA and/or LAMA without ICS** • Avoid maintenance OCS	• **TREAT AS COPD (see GOLD report)** - Initially LAMA and/or LABA - Add ICS as per GOLD for patients with hospitalizations, ≥2 exacerbations/year requiring OCS, or blood eosinophils ≥300/µl • Avoid high dose ICS, avoid maintenance OCS • Reliever containing ICS is not recommended

REVIEW PATIENT AFTER 2-3 MONTHS. REFER FOR EXPERT ADVICE IF DIAGNOSTIC UNCERTAINTY OR INADEQUATE RESPONSE

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma (N Engl J Med 2022; 386:2071-2083)

- A multinational, phase 3, double-blind, randomized, event-driven trial to evaluate the efficacy and safety of albuterol–budesonide, as compared with albuterol alone, as rescue medication in patients with uncontrolled moderate-to-severe asthma who were receiving inhaled glucocorticoid-containing maintenance therapies, which were continued throughout the trial. **Adults and adolescents (≥12 years of age) were randomly assigned in a 1:1:1 ratio to one of three trial groups: a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide** (with each dose consisting of two actuations of 90 µg and 80 µg, respectively [the higher-dose combination group]), **a fixed-dose combination of 180 µg of albuterol and 80 µg of budesonide** (with each dose consisting of two actuations of 90 µg and 40 µg, respectively [the lower-dose combination group]), **or 180 µg of albuterol (with each dose consisting of two actuations of 90 µg** [the albuterol-alone group]). **Children 4 to 11 years of age were randomly assigned to only the lower-dose combination group or the albuterol-alone group.** The **primary efficacy end point was the first event of severe asthma exacerbation** in a time-to-event analysis, which was performed in the intention-to-treat population.



Efficacy and Safety of Albuterol/Budesonide (PT027) in Mild-to-Moderate Asthma: Results of the DENALI Study

(Am J Respir Crit Care Med 2022;205:A3414)

- The Phase 3 DENALI study evaluated contributions of the mono-components to **albuterol/budesonide efficacy in patients with mild-to-moderate asthma ≥4 years. Patients ≥12 years were randomized 1:1:1:1:1 to four-times-daily albuterol/budesonide 180/160 or 180/80 µg, albuterol 180 µg, budesonide 160 µg or placebo for 12 weeks**; patients 4-11 years were not included in this analysis set. **Dual-primary endpoints were change from baseline in forced expiratory volume in 1 second area under the curve from 0-6 hours (FEV1 , AUC0-6h) over 12 weeks and in trough FEV1 at Week 12.**
- Of 1001 patients randomized, 989 were aged ≥12 years (mean age 48.9 years, 62.2% female). **Change from baseline in FEV1 AUC0-6h over 12 weeks was greater with albuterol/budesonide 180/160 µg difference 80.7 mL**, 95% confidence interval [CI] 28.4-132.9; **p=0.003**).
- **Change in trough FEV1 at Week 12 was greater with albuterol/budesonide** 180/160 and 180/80 µg versus albuterol (LSM **difference 132.8 mL** [95% CI 63.6-201.9] **and 120.8 mL** [95% CI 51.5-190.1], **respectively; both p<0.001).**
- **Conclusions: Both mono-components contributed to albuterol/budesonide efficacy, with the combinations demonstrating superior effects on lung function. Onset and duration of bronchodilation were similar for albuterol/budesonide vs albuterol on Day 1, and more patients experienced a nominal improvement in asthma control at Week 12.**

Albuterol–Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma – MANDALA Trial (N Engl J Med 2022; 386:2071-2083)

- RESULTS - A total of 3132 patients underwent randomization, among whom 97% were 12 years of age or older. **The risk of severe asthma exacerbation was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74**; 95% confidence interval [CI], 0.62 to 0.89; P=0.001). **The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P=0.052). The incidence of adverse events was similar in the three trial groups.**
- CONCLUSIONS - The risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies.

- **FDA approved 1-10-2023**
- **AIRSUPRA is a combination of albuterol, a beta2-adrenergic agonist and budesonide, indicated for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older.**
- Recommended Dosage: AIRSUPRA 180 mcg/160 mcg (administered as 2 actuations of albuterol/budesonide 90 mcg/80 mcg) by oral inhalation as needed for asthma symptoms.
- Maximum of 6 doses (12 inhalations) in a 24-hour period.
- Cost:

Global Initiative for Chronic Obstructive Lung Disease

2023 Teaching Slide Set

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

Bronchodilators in Stable COPD

Table 3.4

2023 Teaching Slide Set

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms **(Evidence A)**
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms **(Evidence A)** IE. **albuterol/ipratropium - Combivent** vs. albuterol
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy **(Evidence A)** **Umeclidinium/ Vilanterol (Anoro®), Tiotropium/Olodaterol (Stiolto®) QD** Glycopyrrolate/Formoterol (Bevespi®) and Glycopyrronium/Indacaterol (Ultibron®) BID
- Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy **(Evidence B)**
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**
- Single inhaler therapy may be more convenient and effective than multiple inhalers

Anti-Inflammatory Therapy in Stable COPD

Table 3.5

2023 Teaching Slide Set

Inhaled Corticosteroids	• An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD **(Evidence A)** • Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)** • Lower blood and sputum eosinophils are associated with greater presence of proteobacteria, notably *Haemophilus*, increased bacterial infections & pneumonia • Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia **(Evidence C)** • Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy **(Evidence A)**. Recent data suggest a beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations • Single inhaler therapy may be more convenient and effective than multiple inhalers
Oral Glucocorticoids	• Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**
PDE4 Inhibitors	• In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations: • A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)** • A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA+ICS combinations **(Evidence A)**

Factors to Consider when Initiating ICS Treatment

Figure 3.1

2023 Teaching Slide Set

Factors to consider when adding ICS to long-acting bronchodilators:
(note the scenario is different when considering ICS withdrawal)

STRONGLY FAVORS USE	History of hospitalization(s) for exacerbations of COPD[#]
	≥ 2 moderate exacerbations of COPD per year[#]
	Blood eosinophils ≥ 300 cells/μL
	History of, or concomitant asthma
FAVORS USE	1 moderate exacerbation of COPD per year[#]
	Blood eosinophils 100 to < 300 cells/μL
AGAINST USE	Repeated pneumonia events
	Blood eosinophils < 100 cells/μL
	History of mycobacterial infection

[#]despite appropriate long-acting bronchodilator maintenance therapy (see Table 3.4 and Figure 4.3 for recommendations);
*note that blood eosinophils should be seen as a continuum; quoted values represent approximate cut-points; eosinophil counts are likely to fluctuate.

Adapted from & reproduced with permission of the © ERS 2019: *European Respiratory Journal 52 (6) 1801219; DOI: 10.1183/13993003.01219-2018 Published 13 December 2018*

Evidence Supporting a Reduction in Mortality with Pharmacotherapy and Non-pharmacotherapy in COPD Patients

Table 3.6

2023 Teaching Slide Set

Therapy	RCT*	Treatment effect on mortality	Patient characteristics
Pharmacotherapy			
LABA+LAMA+ICS[1]	Yes	Triple compared to dual LABD relative risk reduction: IMPACT HR 0.72 (95% CI: 0.53, 0.99) ETHOS HR 0.51 (95% CI: 0.33, 0.80)	Symptomatic people with a history of frequent and/or severe exacerbations
Non-Pharmacological Therapy			
Smoking (Sm) Cessation[2]	Yes	8.83/1000 person-years (Sm cessation) vs 10.38/1000 person-years (UC) (p = 0.03)	Asymptomatic or mildly symptomatic
Pulmonary Rehabilitation (PR)[3]	Yes	After early PR: RR 0.58 (95% CI 0.35, 0.98) and at the longest follow-up RR 0.55 (95% CI 0.12, 2.57)	Hospitalized for exacerbations of COPD (during or ≤ 4 weeks post d/c)
LTOT[4]	Yes	NOTT, ≥ 19 hours of continuous oxygen vs ≤ 13 hours: 50% reduction MRC, ≥ 15 hours vs no oxygen: 50% reduction	PaO_2 ≤ 55 or < 60 mmHg with *cor pulmonale* or secondary polycythemia
NPPV[5]	Yes	12% in NPPV (high IPAP level) and 33% in control (HR 0.24; 95% CI 0.11, 0.49)	Stable COPD with marked hypercapnia
LVRS[6]	Yes	0.07 deaths/person-year (LVRS) vs 0.15 deaths/person-year (UC) RR for death 0.47 (p = 0.005)	Upper lobe emphysema and low exercise capacity

*RCT with pre-specified analysis of the mortality outcome (primary or secondary outcome)

1. IMPACT and ETHOS trials (Lipson et al. 2020; Martinez et al. 2021). 2 Lung Health Study (Anthonisen et al. 2005). 3. Review and meta-analysis (Ryrso et al. 2018) 4. NOTT and MRC trials (NOTT 1980; MRC 1981) 5. Kohlein et al., trial (Kohlein et al. 2014) 6. NETT trial (Fishman et al. 2003)

ICS: inhaled corticosteroid; LABA: long-acting B2-agonist; LAMA: long acting anti-muscarinic; LTOT: long-term oxygen therapy; NPPV: noninvasive positive pressure ventilation; LVRS: lung volume reduction surgery; UC: usual treatment control group.

IMPACT Trial – Fluticasone furoate/vilanterol/umeclidinium – Trelegy Ellipta by GSK
Am J Respir Crit Care Med 2020; 201(12): 1508-16

ETHOS Trial – Budesonide/formoterol/glycopyrrolate - Breztri Aerosphere by AZ
N Engl J Med 2020; 383(1): 35-48.

Triple Inhaled LABA/LAMA/ICS Therapy

TRELEGY ELLIPTA ® (fluticasone furoate, umeclidinium, and vilanterol inhalation powder), for oral inhalation
Once a day dosing

BREZTRI AEROSPHERE® (budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol **device changes:**
-The inhaler device is bright yellow
-More accurate puff indicator means patients will know exactly how many doses they have left
-Upgraded cap designed to prevent unintended discharge of medicine
- **BID dosing**

©

Key Points for the Use of Bronchodilators

Table 4.6

2023 Teaching Slide Set

- LABAs and LAMAs are preferred over short-acting agents except for patients with only occasional dyspnea **(Evidence A)**, and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- When initiating treatment with long acting bronchodilators the preferred choice is a combination of a long-acting muscarinic antagonist and a long acting ß2-agonist. In patients with persistent dyspnea on a single long acting bronchodilator treatment should be escalated to two **(Evidence A)**. The combination can be given as single inhaler or multiple inhaler treatment
- Inhaled bronchodilators are recommended over oral bronchodilators **(Evidence A)**
- Theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable **(Evidence B)**

Key Points for the Use of Anti-Inflammatory Agents

Table 4.7

2023 Teaching Slide Set

- Long-term monotherapy with ICS is not recommended **(Evidence A)**
- We do not encourage the use of a LABA+ICS combination in COPD. If there is an indication for an ICS the combination LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore the preferred choice. This combination can be given as single or multiple inhaler therapy.
- If patients with COPD have features of asthma, treatment should always contain an ICS
- In patients with severe to very severe airflow limitation, chronic bronchitis and exacerbations the addition of a PDE4 inhibitor to a treatment with long acting bronchodilators with/without ICS can be considered **(Evidence B)**
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, macrolides, in particular azithromycin, can be considered **(Evidence B)**
- Statin therapy and/or beta-blockers are not recommended for prevention of exacerbations **(Evidence A)**

Key Points for the Use of Other Pharmacological Treatments

Table 4.8

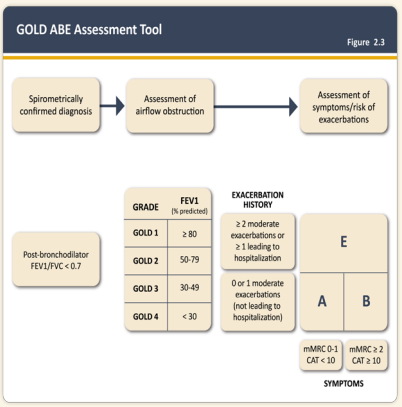
2023 Teaching Slide Set

- Patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy **(Evidence B)**
- Antitussives cannot be recommended **(Evidence C)**
- Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD **(Evidence B)**
- Low-dose long acting oral and parenteral opioids may be considered for treating dyspnea in COPD patients with severe disease **(Evidence B)**

GOLD ABE Assessment Tool

Figure 2.3

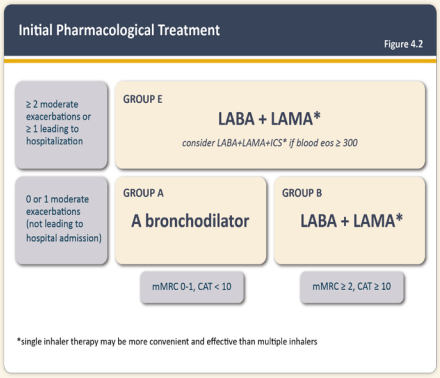
2023 Teaching Slide Set



Initial Pharmacological Treatment

Figure 4.2

2023 Teaching Slide Set



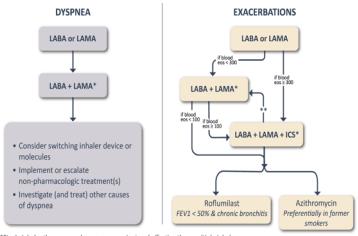
*single inhaler therapy may be more convenient and effective than multiple inhalers

Follow-up Pharmacological Treatment

Figure 4.4

2023 Teaching Slide Set

1. IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.
2. IF NOT:
   - Check adherence, inhaler technique and possible interfering comorbidities
   - Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - Place patient in box corresponding to current treatment & follow indications
   - Assess response, adjust and review
   - These recommendations do not depend on the ABE assessment at diagnosis



*Single inhaler therapy may be more convenient and effective than multiple inhalers

**Consider de-escalation of ICS if pneumonia or other considerable side-effects. In case of blood eos ≥ 300 cells/µl de-escalation is more likely to be associated with the development of exacerbations

Key Points for the Management of Exacerbations

Table 5.5

2023 Teaching Slide Set

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**
- Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not normally be more than 5 days **(Evidence A)**
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should normally be 5 days **(Evidence B)**
- Methylxanthines are not recommended due to increased side effect profiles **(Evidence B)**
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival **(Evidence A)**

Prednisone 40 mg daily x 5 days. REDUCE trial (JAMA 2013 Jun 5;309:2223) demonstrated prednisone 40 mg po x 5 days non-inferior to 14 days for re-exacerbation in next 6 months.

Current guidelines do not recommend use of antibiotics in general but do recommend antibiotic therapy for moderately or severely ill patients with AECOPDs who have three cardinal symptoms (increase in dyspnea, sputum volume, and sputum purulence), or who have two of the cardinal symptoms including purulence of sputum, or who require mechanical ventilation (invasive or non-invasive).

SELF EVALUATION

Pharmacotherapy Update - Parts 1-2

1. T/F - Use of Recombinant Zoster Vaccine/Shingrix is now recommended in Immunocompromised Patients Aged ≥19 Years

2. T/F - Adults aged ≥65 years who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.

3. T/F - The CDC recommends for people 65 years and older, there are three flu vaccines that are preferentially recommended over other flu vaccines: Fluzone High-Dose Quadrivalent inactivated flu vaccine, FluBlok Quadrivalent recombinant flu vaccine, and Fluad Quadrivalent adjuvanted inactivated flu vaccine.

4. According to the 2023 ADA Standards of Care The quantity of sleep is known to be associated (in a U-shaped manner) with health outcomes (e.g., obesity and HbA1c), with both long (>?) and short (<?) sleep durations having negative impacts.
    a. < 5 hrs, >7 hrs
    b. < 6 hrs, > 8 hrs
    c. < 7 hrs, > 9 hrs
    d. < 8 hrs, > 10 hrs

5. T/F - According to the 2023 ADA Standards of Care - In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible and if insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit.

6. T/F - According to the 2023 ADA Standards of Care an ACE inhibitor or an angiotensin receptor blocker is recommended for all patients with diabetes with or without diabetic kidney disease or hypertension.

7. According to the 2022 Global Initiative for Asthma (GINA) Guidelines the preferred reliever or rescue inhaler for adults and adolescents 12 and older is?
    a. Albuterol (Ventolin/Proair)
    b. Albuterol plus ipratropium (Combivent)
    c. Salmeterol plus fluticasone propionate (Advair)
    d. Formoterol plus inhaled corticosteroid (Symbicort or Dulera)

8. T/F - According to the 2023 GOLD Guidelines for COPD the preferred medication for improvement of FEV1 and reducing symptoms in a patient with COPD is the combination of a SABA and a SAMA (albuterol plus ipratropium as in Combivent Respimat) as the combination is more effective than either agent alone.

9. T/F - According to the 2023 GOLD Guidelines for COPD the preferred medication for reducing symptoms in a patient with COPD in Group B is the combination of a LABA plus LAMA (i.e. tiotropium/olodaterol – Stioloto Respimat or umeclidinium/vilanterol – Anoro Ellipta)

10. T/F - According to the 2023 GOLD Guidelines for COPD the preferred medication for reducing symptoms in a patient with COPD in Group E who has blood eosinophils <100 cells/ul and no history of hospitalization for COPD exacerbation is a combination of a LABA plus LAMA plus ICS (i.e. vilanterol, umeclidinium, and fluticasone furoate – Trelegy Ellipta or formoterol fumarate, glycopyrrolate, and budesonide – Breztri Aerosphere)

Answer Key: 1. T, 2. T, 3. T, 4. B, 5. T, 6. F, 7. D, 8. T, 9. T, 10. F

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Stephanie P. Ottenwess, Esq., of Southfield, Michigan, is the managing partner of Ottenwess Law, a boutique firm serving a diverse clientele in litigation, regulatory and transactional matters with particular focus on medical malpractice, professional liability defense and health law. Her healthcare practice includes counseling on transactional matters, licensing and healthcare litigation, as well as federal and state healthcare regulatory compliance including Stark, self-referral, and Anti-Kickback laws. Ms. Ottenwess' clients include executives, physicians and physician groups, hospitals, practice managers and other healthcare professionals. She also speaks and authors articles on legal issues impacting the healthcare industry.

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Understanding and Avoiding Healthcare Fraud, Waste & Abuse - Parts 1 & 2

HEALTHCARE FRAUD IS A SERIOUS PROBLEM

The Government spends almost a trillion dollars each year on the Medicare and Medicaid programs.

Healthcare fraud is estimated to cost taxpayers $30 billion to $100 billion each year.

An array of laws has been enacted to combat fraud, waste, and abuse and protect the integrity of the healthcare payment system.

OTTENWESSLAW

FRAUD

- Knowingly submitting false or fraudulent information to get a benefit that you are not entitled to receive. Knowingly does NOT mean that the person submitting the claim must have actual knowledge the claim is false. A person acting in reckless disregard or in deliberate ignorance of the truth can be found liable as well.
- It is a criminal offense to knowingly defraud a healthcare program.
- Some examples of fraud:
  - Billing for services, prescriptions or supplies not provided
  - Billing for the same services more than once (duplication)
  - Billing for a higher level of service than was actually provided (up-coding)
  - Billing separately for services that should be a single service (unbundling)

OTTENWESSLAW

WASTE

- Overusing services or other practices that result in unnecessary costs to federal healthcare programs. Waste is generally considered to be the misuse of resources due to improper management, practices, or controls.
- Some examples of Waste:
  - Ordering multiple tests when only one is necessary
  - Prescribing brand name drugs when generics are available
  - Prescribing more medications than necessary
  - Scheduling too many office visits

OTTENWESSLAW

ABUSE

- Excessive or improper use of government resources (including funds) that are inconsistent with generally accepted practices, but where the provider has not knowingly or intentionally misrepresented facts to obtain payment.
- Some examples of Abuse:
  - Billing for services that are not medically necessary
  - Billing for brand name drugs when generics are dispensed
  - Charging excessively for services or supplies

OTTENWESSLAW

KEY FRAUD AND ABUSE LAWS

False Claims Act	Anti-Kickback Statute	Physician Self-Referral Statute ("Stark")	Exclusion Statute	Civil Monetary Penalties Law

OTTENWESSLAW

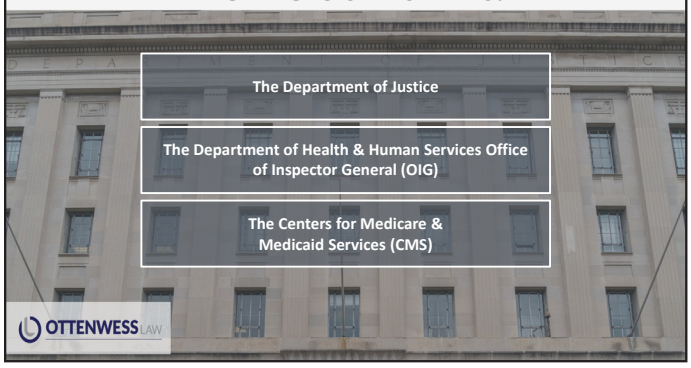
BUT, DON'T FORGET ABOUT THESE. ..

State laws

Provider contracts

OTTENWESSLAW

WHO ENFORCES THESE LAWS?



- The Department of Justice
- The Department of Health & Human Services Office of Inspector General (OIG)
- The Centers for Medicare & Medicaid Services (CMS)

OTTENWESS LAW

FALSE CLAIMS ACT

- Prohibits the submission of false or fraudulent claims to the Federal Government
  - Claims may be false if
    - The service is not actually rendered to the patient
    - The service is provided but already covered under another claim
    - The service is miscoded
    - The services is not supported by the medical record

  Must report and repay an overpayment within the latter of 60 days or date cost report is due. (31 USC 3729; 42 USC 1320a-7a(a); 42 CFR 1003.200)

OTTENWESS LAW

FALSE CLAIMS ACT

- You do not have to *intend* to defraud the Government to violate the FCA
- You can be punished if you act with deliberate ignorance or reckless disregard of the truth
  - You cannot hide your head in the sand and avoid liability!

OTTENWESS LAW

FALSE CLAIMS ACT

- Civil Penalties
  - Repayment plus interest
  - Civil monetary penalties of $13,508* to $27,018* per claim
  - Admin penalty $23,996* per claim failed to return
  - 3x damages
  - Exclusion from Medicare/Medicaid
- Criminal Penalties:
  - Imprisonment
  - Criminal fines

(42 USC 1320a-7a(a); 18 USC 287; 42 CFR 1003.210; 45 CFR 102.3; 86 FR 70740)

OTTENWESS LAW

FALSE CLAIMS ACT

- Whistleblowers
- FCA provision that allows a private individual to file a lawsuit on behalf of the U.S.
  - Provides a strong financial incentive to whistleblowers to report fraud
    - Can receive up to 30% of any FCA recovery

Whistleblowers can be… Ex-business partners, hospital or office staff, competitors, or even patients.

OTTENWESS LAW

ANTI-KICKBACK STATUTE

- Criminal Statute
- Cannot knowingly and willfully offer, pay, solicit or receive remuneration to induce referrals for items or services covered by Federal health care program unless transaction fits within a regulatory safe harbor. (42 USC 1320a-7b(b); 42 CFR 1003.300(d))
- Remuneration includes anything of value; not just cash.
  - Free rent, expensive hotel stays; excessive compensation for medical directorships
- "One purpose" test (US v. Greber (1985))

Penalties

- Felony
- 10 years in prison
- $100,000 criminal fine
- Civil monetary penalties
- 3x damages
- Exclusion from Medicare/Medicaid
- *Automatic False Claims Act violation*
- 42 USC 1320a-7a(a)(7); 42 USC 1320a-7b(b); 42 CFR 1003.310; 45 CFR 102.3

OTTENWESS LAW

ANTI-KICKBACK STATUTE

Kickbacks can lead to:

- Overutilization
- Increased costs
- Corruption of medical decision making
- Patient steering
- Unfair competition

OTTENWESS LAW

ANTI-KICKBACK STATUTE:

SAFE HARORS

- Bona fide employment
- Personal services contracts
- Leases for space or equipment
- Investments in group practice
- Investments in ASCs
- Sale of practice
- Recruitment
- Certain investment interests

- Waiver of beneficiary coinsurance and deductible amounts.
- Transportation programs
- OB malpractice insurance subsidies
- Electronic health record items or services
- Cybersecurity technology
- Warranties
- Discounts

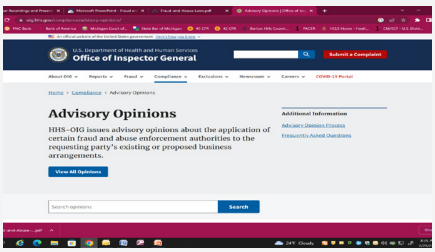
- Electronic health record items or Value-based care arrangements
- Care coordination arrangements
- Patient engagement incentive
- 42 CFR 1001.952
- OIG's Safe Harbor Regulations: https://oig.hhs.gov/compliance/safe-harbor-regulations/

OTTENWESS LAW

OIG may issue advisory opinions.
Listed on OIG fraud and abuse website, www.oig.hhs.gov/fraud.

Not binding on anyone other than the participants to the opinion.

But you are fairly safe if you act consistently with a favorable advisory opinion



OTTENWESS LAW

PHYSICIAN SELF-REFERRAL LAW (STARK)

- If the physician (or family member) has a financial relationship with the entity:
  - Physician may not refer patients to entity for designated health services ("DHS"), and
  - Entity may not bill Medicare or Medicaid for such DHS unless the arrangement fits within a regulatory exception (safe harbor).
  - Financial relationship includes both ownership/investment interests and compensation arrangements
  - Strict liability statute: proof of specific intent to violate law not required! (42 USC 1395nn; 42 CFR 411.353; 1003.300)

Penalties

- No payment for services provided per improper referral.
- Repayment w/in 60 days.
- Civil penalties. – $28,000* per claim – $175,000* per scheme
- 42 CFR 411.353, 1003.310; 45 CFR 102.3

Likely False Claims Act violation
Likely Anti-Kickback Statute violation

OTTENWESS LAW

STARK

This applies to referrals by a physician to entities with which the physician (or their family member) has a financial relationship.

- Physician = as defined in 42 USC 1395x(r), i.e.,
- MDs
- DOs
- Oral surgeons
- Dentists
- Podiatrists
- Optometrists
- Chiropractors
- (42 CFR 411.351)

- Family member =
  - Spouse
  - Parent, child
  - Sibling
  - Stepparent, stepchild, stepsibling
  - Grandparent, grandchild
  - In-law

OTTENWESS LAW

STARK

- Applies to referrals for designated health services ("DHS") payable in whole or part by Medicare or Medicaid.
- Inpatient and outpatient hospital services
- Outpatient prescription drugs
- Clinical laboratory services
- Physical, occupational, or speech therapy
- Home health services
- Radiology and certain imaging services

- Radiation therapy and supplies
- Durable medical equipment and supplies
- Parenteral and enteral nutrients, equipment, and supplies
- Prosthetics and orthotics
- Check definitions to confirm scope and exceptions.
- CMS website lists some of the affected CPT codes.
  - (42 CFR 411.351)

OTTENWESS LAW

STARK SAFE HARBORS: OWNERSHIP

Must satisfy all the requirements to receive safe harbor protection

- **Ownership & Compensation Arrangements**
  - Physician services
  - In-office ancillary services
  - Prepaid health plans
  - Academic medical centers
  - Implants by an ASC
  - EPO and dialysis drugs
  - Preventative screening tests, immunizations and vaccines
  - Eyeglasses and contact lenses following surgery (42 CFR 411.355)

- **Ownership Arrangements**
  - Publicity traded securities
  - Mutual funds
  - Rural providers
  - Whole hospital
  - Intra-family rural referrals
  - Others
  - (42 CFR 411.356)

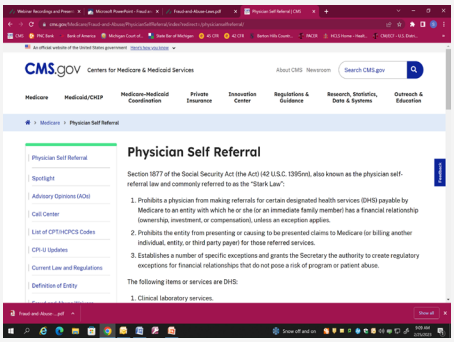
OTTENWESS LAW

STARK SAFE HARBORS: COMPENSATION

- Employment
- Personal services contracts
- Remuneration to physician <$5000/yr
- FMV
- Space or equipment leases
- Timeshare arrangements
- Recruitment and retention
- Non-monetary comp up to $429
- Medical staff incidental benefits
- Professional courtesy
- OB malpractice subsidies

- Isolated transactions
- Payments by a physician
- Charitable donations by a physician
- Compliance training
- Indirect compensation arrangements
- Referral services
- Health information tech and support
- Cyber security technology
- Valued-based comp arrangements
- (42 CFR 411.357)

OTTENWESS LAW



OTTENWESS LAW

EXCLUSION FROM MEDICARE & MEDICAID

- Under the Exclusion Authorities, OIG may exclude providers from participation in the Federal health care programs.
  - [42 USC 1320a-7]
    - » Mandatory Exclusions
    - » Permissive Exclusions

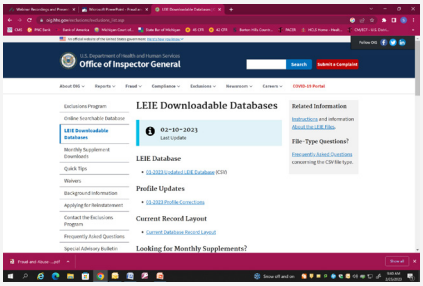
OTTENWESS LAW

CIVIL MONETARY PENALTIES LAW

- Prohibits certain specified conduct, e.g.:
- Submitting false or fraudulent claims, misrepresenting facts relevant to services, or engaging in other fraudulent practices.
- Violating Anti-Kickback Statute or Stark law.
- Violating EMTALA.
- Failing to report and repay an overpayment.
- Failing to report adverse action against providers.
- Offering inducements to program beneficiaries.
- Offering inducements to physicians to limit services.
- Submitting claims for services ordered by, or contracting with, an excluded entity.
- 42 USC 1320a-7a; 42 CFR 1003.200-1100
  - Penalties range from $10,000-$50,000 per violation; Exclusion from Medicare & Medicaid

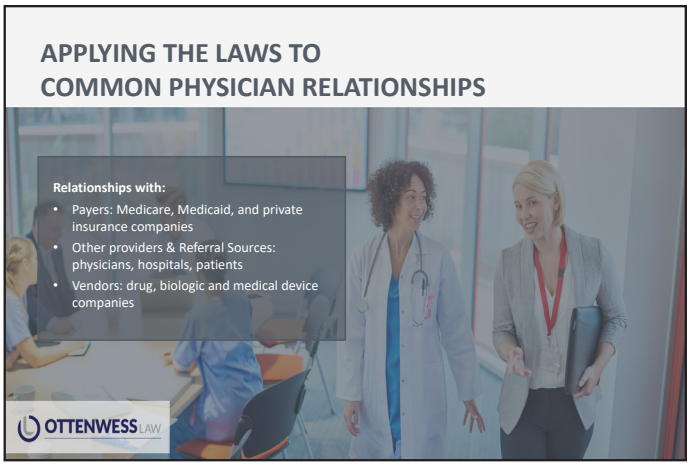
OTTENWESS LAW

CHECK THE LEIE REGULARLY!

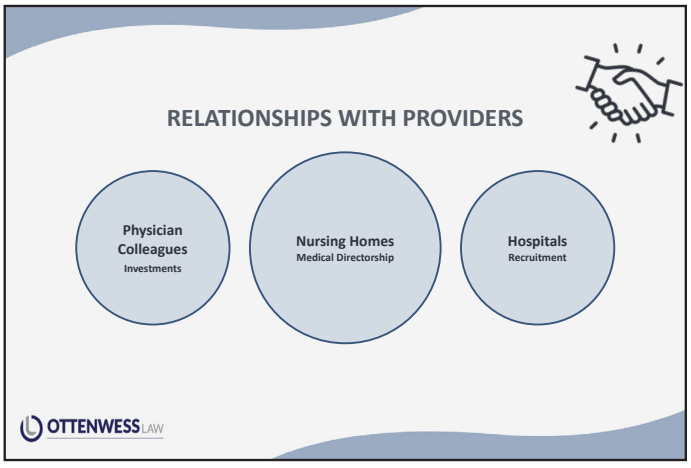


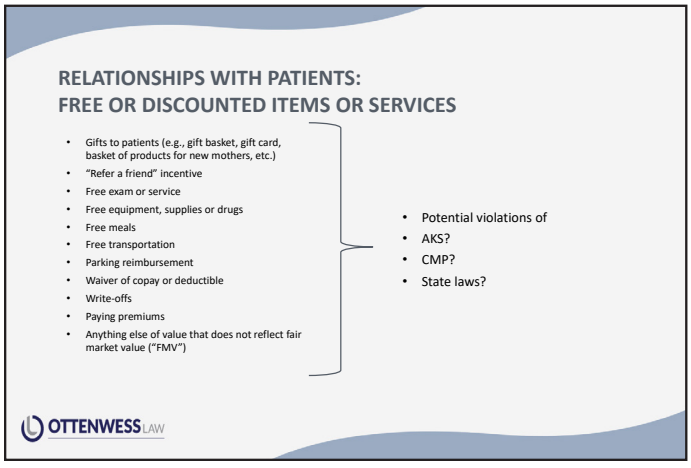
OTTENWESS LAW

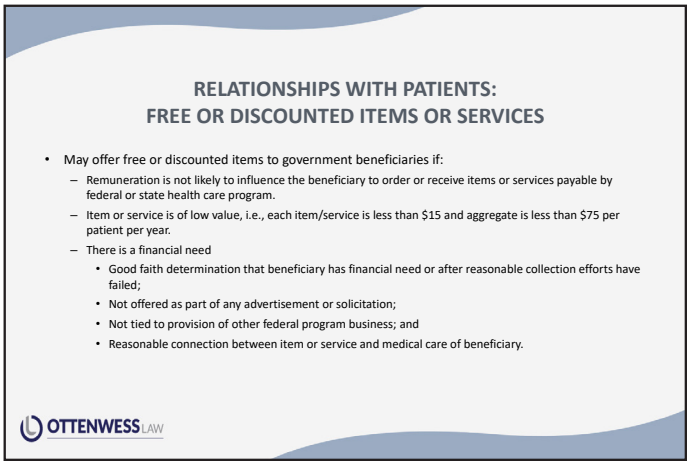

DON'T FORGET!
Other Federal Statutes
State Laws
Private Payors
OTTENWESS LAW


APPLYING THE LAWS TO
COMMON PHYSICIAN RELATIONSHIPS
Relationships with:
• Payers: Medicare, Medicaid, and private insurance companies
• Other providers & Referral Sources: physicians, hospitals, patients
• Vendors: drug, biologic and medical device companies
OTTENWESS LAW


PAYERS
• Fraudulent billings – accurately documenting the services you provide
• Proper Coding and Billing
• Maintain accurate and complete medical records to support payment of claims
• Good documentation is a must!
OTTENWESS LAW


RELATIONSHIPS WITH PROVIDERS
Physician Colleagues
Investments
Nursing Homes
Medical Directorship
Hospitals
Recruitment
OTTENWESS LAW


RELATIONSHIPS WITH PATIENTS:
FREE OR DISCOUNTED ITEMS OR SERVICES
• Gifts to patients (e.g., gift basket, gift card, basket of products for new mothers, etc.)
• "Refer a friend" incentive
• Free exam or service
• Free equipment, supplies or drugs
• Free meals
• Free transportation
• Parking reimbursement
• Waiver of copay or deductible
• Write-offs
• Paying premiums
• Anything else of value that does not reflect fair market value ("FMV")
• Potential violations of
• AKS?
• CMP?
• State laws?
OTTENWESS LAW


RELATIONSHIPS WITH PATIENTS:
FREE OR DISCOUNTED ITEMS OR SERVICES
• May offer free or discounted items to government beneficiaries if:
– Remuneration is not likely to influence the beneficiary to order or receive items or services payable by federal or state health care program.
– Item or service is of low value, i.e., each item/service is less than $15 and aggregate is less than $75 per patient per year.
– There is a financial need
• Good faith determination that beneficiary has financial need or after reasonable collection efforts have failed;
• Not offered as part of any advertisement or solicitation;
• Not tied to provision of other federal program business; and
• Reasonable connection between item or service and medical care of beneficiary.
OTTENWESS LAW

RELATIONSHIPS WITH VENDORS

- Free drug samples
- Promotional speaking
- Gifts and gift reporting requirements

OTTENWESS LAW

ACTION ITEMS

OTTENWESS LAW

CHECK YOUR RELATIONSHIPS

With Patients & Referral Sources

- Billing Policies
  - Waiving copays
  - Write-offs
  - Prompt pay or self-pay discounts
  - Free or discounted items
- Contracts and leases
  - Fair market value
  - Compensation not based on referrals
  - Services actually provided

With Payors & Vendors

- Overpayments or payment for items not provided
- Accurate coding, billing, records
- Proper handling of drug samples
- Proper consulting agreements
- Transparency in relationships

OTTENWESS LAW

COMPLIANCE PLAN

Actually have a Compliance Plan!

- Ensure it has required elements
- Policies, procedures and standards of conduct
- Designated compliance officer and committee
- Conduct effective training and education
- Develop effective lines of communication, e.g., complaint hotline
- Conduct internal monitoring and auditing
- Enforce through publicized disciplinary guidelines
- Respond promptly to offenses and implement corrective action.
- See OIG's Compliance Program Guidance documents Available at https://oig.hhs.gov/compliance/compliance-guidance/

OTTENWESS LAW

TRAIN KEY PERSONNEL

Include the following people:

- Administration.
- Compliance officers and committees.
- Human resources.
- Physician relations and medical staff officers.
- Marketing / public relations.
- Governing board members.
- Purchasing.
- Accounts payable.
- Document training.
- Review and repeat.

OTTENWESS LAW

IF YOU THINK YOU HAVE A PROBLEM

- Suspend payments or claims until resolved.
- Investigate the problem per the compliance plan.
- Consider involving an attorney to maintain privilege.
- Unwind the problematic investment.
- Disentangle yourself from the suspicious relationship.
- Implement appropriate corrective action.
- But remember that prospective compliance may not be enough.
- If repayment is due:
  - Report and repay per applicable law.
  - Self-disclosure program.
  - To OIG, if there was a knowing violation of FCA, AKS, or CMPL.
  - To CMS, if there was a violation of Stark.

OTTENWESS LAW

SELF EVALUATION

Understanding and Avoiding Healthcare Fraud, Waste & Abuse - Parts 1 & 2

1. T/F - Healthcare fraud is a serious problem that is estimated to cost taxpayers billions of dollars each year.

2. T/F - Only federal laws prohibit healthcare fraud.

3. Which one of the following federal government entities enforces laws in healthcare?

a. Office of Inspector General (OIG)
b. Internal Revenue Services (IRS)
c. Government Accountability Office (GAO)
d. Central Intelligence Agency (CIA)

4. Fraud can include:

a. Billing for services, prescriptions or supplies not provided
b. Billing for the same services more than once (duplication)
c. Billing for a higher level of service than was actually provided (up-coding)
d. Billing separately for services that should be a single service (unbundling)
e. All of the above

5. Waste can include:

a. Ordering multiple tests when only one is necessary
b. Prescribing brand name drugs when generics are available
c. Prescribing more medications than necessary
d. Scheduling too many office visits
e. All of the above

6. Abuse can include:

a. Billing for services that are not medically necessary
b. Billing for brand name drugs when generics are dispensed
c. Charging excessively for services or supplies
d. All of the above

7. T/F - It is only considered “Fraud” if I actually have knowledge what I am doing is illegal.

8. T/F - Violating the federal fraud and abuse statutes only carries civil penalties.

9. T/F - You should have and follow a robust compliance plan with policies, procedures and standards of conduct applicable to your relationships with Payers (Medicare, Medicaid and private insurance companies); other providers and referral sources; and vendors (drug, biologic and medical device companies) to ensure these relationships are compliant with the fraud and abuse laws.

Answer Key: 1. T, 2. F, 3. A, 4. E, 5. E, 6. D, 7. F, 8. F, 9. T

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Identifying and Treating ADHD

Off-Label Discussion

Bupropion
Desipramine
Duloxetine
Modafinil

Goals

- Develop conviction that adult ADHD is a legitimate clinical entity
- Engender interest in identifying adult ADHD more often **because** of its compelling epidemiologic presence, consequences, and comorbidities
- Enhance confidence in the role of primary care clinicians to Dx and Rx adult ADHD
- Confirm concrete outcomes benefits from Rx

Adult ADHD Management Path

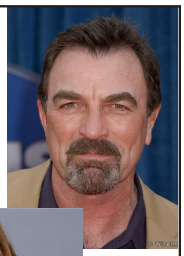
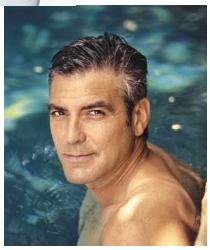
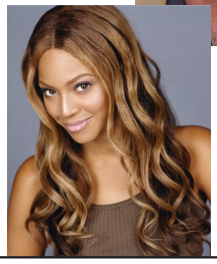
Screening tool (e.g., ASRS)
≥5 DSM Inattention and/or Hyperactivity, onset <12 yrs
Impairment in ≥2 settings ≥6 months
No alternate Dx to Explain Sx
Dx ADHD
No contraindications to Rx
UDT, E-FORSCE, Controlled Substance Agreement
Rx

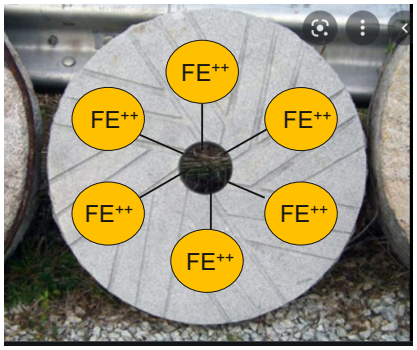
Why Adult ADHD Merits Your Consideration: Current State of the Art

"Most adults with childhood ADHD continue to struggle [with]…employment, post-secondary education, and finances….[and] display high incidence of legal problems, substance abuse, mental health difficulties, and….Despite these impairments, many individuals with ADHD are under-diagnosed in adulthood."

Sibley MH *J Clin Experiment Neurophysiol* 2021;43:340-351

What Do These Folks Have in Common?



Adult ADHD: Is the Dx Legitimate?

- Not a Dx
- Haven for Stimulant Abusers
- Normal Variant
- Legitimate Dx
- A Dx, but OVERdiagnosed
- Excuse for Poor Performance
- Natural Selection Remnant

Perceptions on ADD --Will Krynen, MD

"Among…. the tribes of northern Canada such as the caribou hunters of the McKenzie Basin… adaptive characteristics — constantly scanning the environment, quick decision-making (impulsiveness) and a willingness to take risks — contribute every year to the tribe's survival."

Hartmann T *Attention Deficit Disorder: A Different Perception*
Grass Valley (California): Underwood-Miller Books, 1993

Perceptions on ADD --Will Krynen, MD

"These same behaviors, however, often make it difficult for tribal children to succeed in western schools when we try to impose our western curriculum on them."

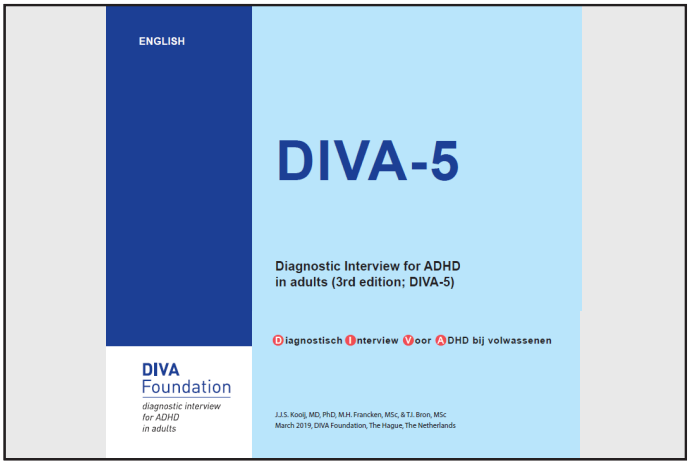
Hartmann T *Attention Deficit Disorder: A Different Perception*
Grass Valley (California): Underwood-Miller Books, 1993

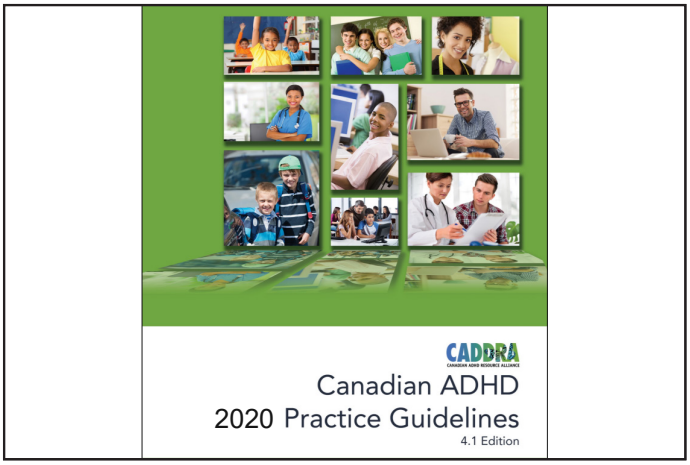
DISORDER VIEW	HUNTER ROLE	FARMER ROLE
Distractible	Constantly monitoring their environment	Not easily distracted from the task at hand
Attention span is short, but can become intensely focused for long periods of time	Able to throw themselves into the chase on a moment's notice	Able to sustain a steady, dependable effort.

Hartmann T *Attention Deficit Disorder: A Different Perception*
Grass Valley (California): Underwood-Miller Books, 1993

DISORDER VIEW	HUNTER ROLE	FARMER ROLE
Poor planner: disorganized and impulsive (makes snap decisions).	Flexible, ready to change strategy quickly	Organized, purposeful. They have a long-term strategy, and they stick to it.
Distorted sense of time: unaware of how long it will take to do something.	Tireless: capable of sustained drives, but only when "hot on the trail" of some goal	Conscious of time and timing. They get things done in time, pace themselves

Hartmann T *Attention Deficit Disorder: A Different Perception*
Grass Valley (California): Underwood-Miller Books, 1993





Is ADHD Overdiagnosed?

"There is a common public misconception, reinforced by much of the media, that ADHD is over-Dx. However, a recent meta-analysis confirmed stable rates of the prevalence of ADHD over the past 30 years."

Canadian ADHD Resource Alliance: *Canadian ADHD Practice Guidelines*, 4.1 Edition, Toronto ON; CADDRA, 2020

Can Primary Care Clinicians Appropriately Manage ADHD?

"…ADHD can be managed in a 1^0 care setting. According to DSM-5, the Dx tasks are to ensure:"

- Current Sx fulfill DSM-5 criteria
- Sx onset by age 12
- Impairments in ≥ 2 life areas
- Impairments present for ≥ 6 months
- No alternate explanation for the Sx/impairment

Canadian ADHD Resource Alliance: *Canadian ADHD Practice Guidelines*, 4.1 Edition, Toronto ON; CADDRA, 2020

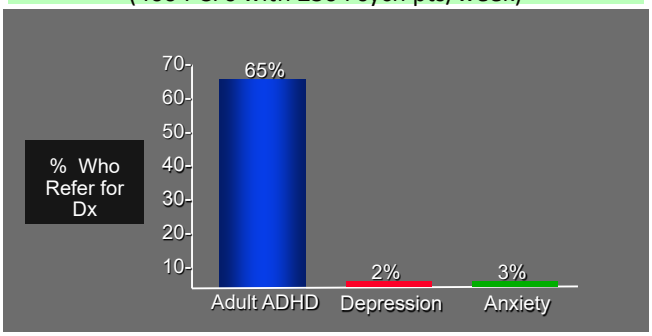
PCP Role in ADHD Dx

"In a survey of 400 PCPs who regularly Rx mental health disorders, approximately half of the respondents reported that they were not confident about diagnosing ADHD in adults and considered the diagnostic criteria for ADHD in adults to be unclear."*

*emphasis added

Goodman DW, Thase ME *Postgrad Med* 2009;121(5):20-30

Adult ADHD: Diagnostic Referral Bias?
(400 PCPs with ≥30 Psych pts/week)



Goodman DW, Thase ME *Postgrad Med* 2009;121(5):20-30

Is Sophisticated Testing Required?

"At this time, there is no evidence that any strategies beyond…the clinical interview in combination with rating scales…offer substantial benefit in the Dx of ADHD."

Canadian ADHD Resource Alliance: *Canadian ADHD Practice Guidelines*, 4.1 Edition, Toronto ON; CADDRA, 2020.

CONSEQUENCES of ADULT ADHD

Impairment of Adult ADHD

"ADHD in adulthood is associated with significant impairment in occupational, academic, and social functioning."

Bukstein O *UpToDate* 2018

Adult ADHD: The Consequences

"The World Health Organization (WHO) rates ADHD as one of the top 10 causes of missed work and reduced work efficiency in the world."

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Adult ADHD: Outcomes

"Compared with age-matched controls, adolescents and adults with ADHD show serious impairment in multiple domains (90% in home lives, 89% in work lives, and 77% in social lives)."

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Adult ADHD: The Consequences

Outcome	ADHD vs Age-Matched Control
Education	Drop out of HS (17% vs 7%)
	Obtain college degree (19% vs 26%)
Employment	More likely to have been fired
	More likely to be unemployed
	Annual salary < $25,000 (39% vs 20%)

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Adult ADHD: The Consequences

Outcome	ADHD vs Age-Matched Control
Interpersonal	Fit well with peers* (40% vs 70%)
	STD's (17% vs 4%)
	Teen Pregnancy (37 X increase)
	Divorce (28% vs 15%)
Driving	Higher rates MVA, Speeding, DUI
	> 3 MVA (26% vs 9%)
	More likely license suspension

*self-appraisal

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

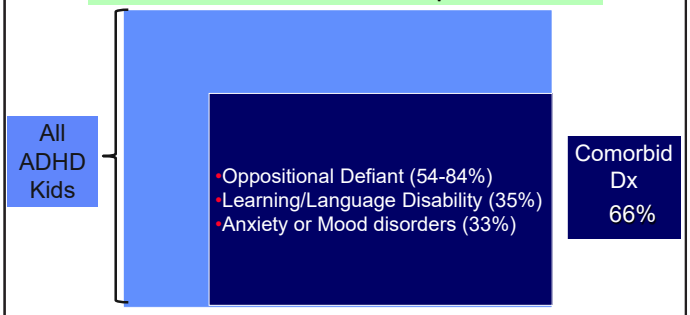
Adult ADHD: The Consequences

Outcome	ADHD vs Age-Matched Control
Legal	2X ↑ likelihood having being arrested*
Comorbidity	Depression ↑
	Social Anxiety (29%)
	Intermittent Explosive Disorder (19.6%)
	↑ Nicotine Dependence*
	Less Successful Smoking Cessation*
	↑ Alcohol, Substance Dependence*

*untreated

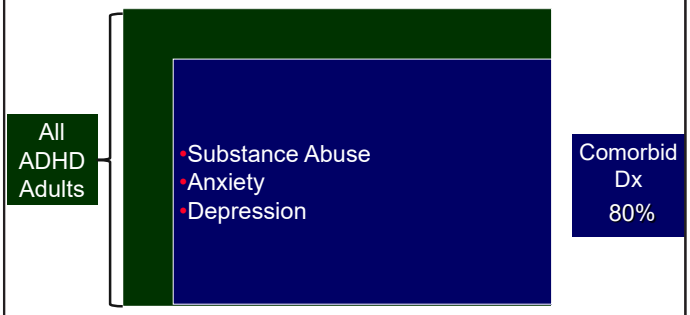
Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Childhood ADHD & Comorbidity The RULE not Exception



Kratochvit C, Wetzel M "ADHD" Conn's Current Therapy 2009 Rakel, Bope, eds (Saunders: Philadelphia)

Adult ADHD & Comorbidity Even More the RULE not Exception



Kratochvit C, Wetzel M "ADHD" *Conn's Current Therapy 2009* Rakel, Bope, eds (Saunders: Philadelphia)

Why Do We Miss the Adult ADHD Dx?

- Comorbidities may overlap or mask ADHD
  - Depression
  - Anxiety
  - Substance Use
- Adult ADHD patients under-report Sx

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Do Adults with ADHD Knock on the Door with ADHD Sx?

"…nearly half the time patients present with a comorbid condition (e.g., depression, anxiety, substance use disorder) and often with chaotic life problems and are not aware that ADHD may be driving their comorbidity."

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

'Resistant' Depression/Anxiety: Consider ADHD

"When a patient appears to have a Rx-resistant depressive or anxiety disorder, with or without persistent difficulty with drug or alcohol abuse or addiction, screening for and treating underlying ADHD may help prevent relapse or recurrence of the comorbid condition(s)."

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Substance Use, Anxiety, Depression, Bipolar: Think ADHD

"…approximately 15%-20% of adults with substance abuse disorders, anxiety, depressive disorders, and bipolar disorders have ADHD."

Wilens TE, Faraone SV, Biederman J "ADHD in Adults" *JAMA* 2004;292(5):619-623

Finding Adult ADHD by Identification of ADHD Kids

- STUDY: Families (n=230) with ≥ 1 child with definite and another with definite/probable DSM-IV ADHD
- METHODS (parents):
  - Structured interviews (videotaped)
  - Multiple psych evaluation tools
- RESULTS (% with lifetime ADHD):
  - One affected parent: 47%
  - Two affected parents: 10%

McGough JJ, et al *Am J Psychiatry* 2005;162:1621-1627

EPIDEMIOLOGY

Adult ADHD Epidemiology

- "It is estimated that around 3-5% of children & about 1-3% of the adult population has ADHD."
- "A meta-analysis of follow-up studies concluded that in up to 65% of children with ADHD, Sx and impairments may persist into adulthood."

Taylor A, Deb S, Unwin G "Scales for the identification of adults with ADHD" a systematic review" *Res Develop Disabil* 2011;32:924-938

ADHD Epidemiology

"In a group of children with ADHD followed from 7 years of age to adulthood, Barkley et al found that approximately 80% still had impairment due to ADHD Sx as adolescents and two-thirds had such impairment as adults."

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Persistence of Childhood ADHD

"Studies have found that a majority of people Dx with ADHD in childhood continue to meet criteria for the disorder as adults."

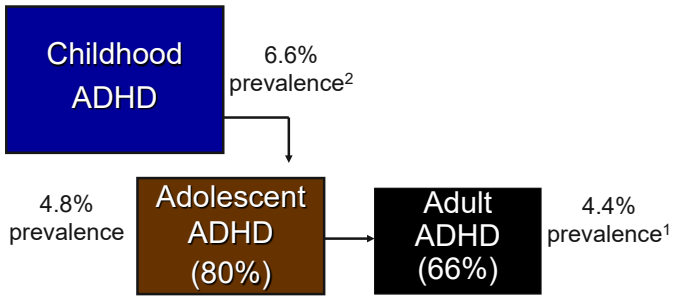
Bukstein O *UpToDate* 2018

Genetics of ADHD

"First degree relatives of ADHD patients have 5 times greater risk of ADHD relative to controls."

Hoffman P, Katz ER *Ferri's Clinical Advisor* 2019:182-183

ADHD Epidemiology



[1]Kessler RC et al *Am J Psychiatry* 2006;163(4):716-723
[2]Barkley RA et al *J Am Acad Child Adolesc Psychiat* 2006;45(2):192-202

Are Self-Referring Patients Gaming Us?

"Some clinicians may be wary of an individual self-referring…they may suspect that the person is looking for drugs….Clinical experience indicates this is an infrequent occurrence."

Canadian ADHD Resource Alliance: *Canadian ADHD Practice Guidelines*, 4.1 Edition, Toronto ON; CADDRA, 2020.

Adult ADHD Management Path

- Screening tool (e.g., ASRS)
- ≥5 DSM Inattention and/or Hyperactivity
- Impairment in ≥2 settings ≥6 months
- No alternate Dx to Explain Sx
- Dx ADHD
- No contraindications to Rx
- UDT, E-FORSCE, Controlled Substance Agreement
- Rx

Adult ADHD Screening and Dx

Adult ADHD Dx Criteria (DSM-V)

- A: ≥5 Sx (inattention or hyperactivity/impulsivity) for ≥6 months
- B: Sx onset prior to age 12
- C: Sx present in multiple settings
- D: Sx create meaningful impairment
- E: Sx not explained by another disorder

Sibley MH *J Clin Experiment Neurophysiol* 2021;43:340-351

ASRS-6

Psychological Medicine, 2005, **35**, 245–256. © 2004 Cambridge University Press
DOI: 10.1017/S0033291704002892 Printed in the United Kingdom

The World Health Organization adult ADHD self-report scale (ASRS): a short screening scale for use in the general population

RONALD C. KESSLER*, LENARD ADLER, MINNIE AMES, OLGA DEMLER, STEVE FARAONE, EVA HIRIPI, MARY J. HOWES, ROBERT JIN, KRISTINA SECNIK, THOMAS SPENCER, T. BEDIRHAN USTUN AND ELLEN E. WALTERS

Department of Health Care Policy, Harvard Medical School; Departments of Psychiatry and Neurology, New York University School of Medicine; Department of Psychiatry, Massachusetts General Hospital; Eli Lilly and Company, Global Health Outcomes; Global Burden of Disease Unit, World Health Organization

Are you living with Adult ADHD?

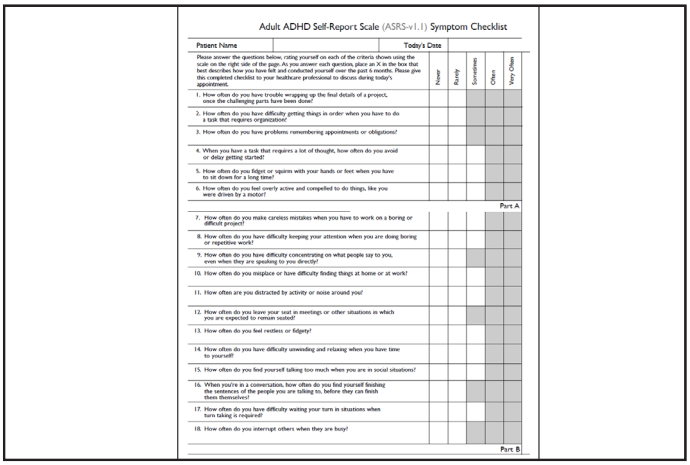
The questions below can help you find out.

Many adults have been living with Adult Attention-Deficit/Hyperactivity Disorder (Adult ADHD) and don't recognize it. Why? Because its symptoms are often mistaken for a stressful life. If you've felt this type of frustration most of your life, you may have Adult ADHD – a condition your doctor can help diagnose and treat.

The following questionnaire can be used as a starting point to help you recognize the signs/symptoms of Adult ADHD but is not meant to replace consultation with a trained healthcare professional. **An accurate diagnosis can only be made through a clinical evaluation.** Regardless of the questionnaire results, if you have concerns about diagnosis and treatment of Adult ADHD, please discuss your concerns with your physician.

This Adult Self-Report Scale-V1.1 (ASRS-V1.1) Screener is intended for people aged 18 years or older.

Adult Self-Report Scale-V1.1 (ASRS-V1.1) Screener
from WHO Composite International Diagnostic Interview
© World Health Organization

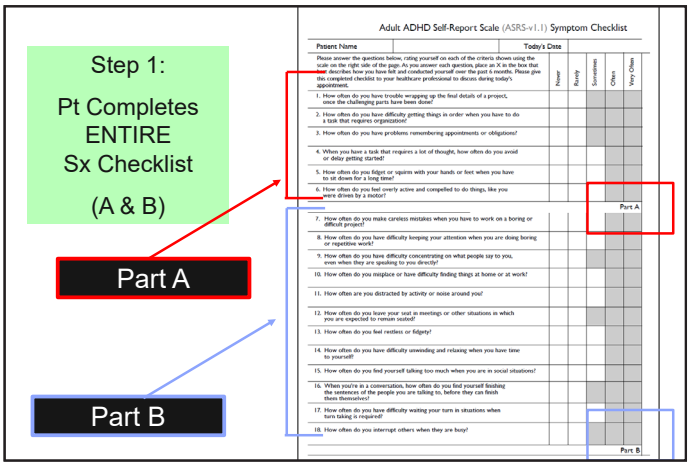


Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name | Today's Date

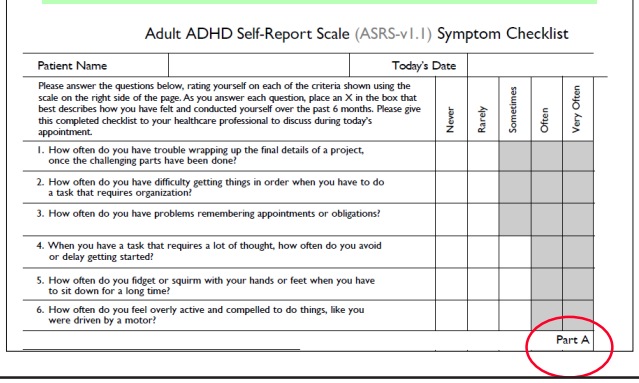
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.

	Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?					
3. How often do you have problems remembering appointments or obligations?					
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?					
Part A					
7. How often do you make careless mistakes when you have to work on a boring or difficult project?					
8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
10. How often do you misplace or have difficulty finding things at home or at work?					
11. How often are you distracted by activity or noise around you?					
12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
13. How often do you feel restless or fidgety?					
14. How often do you have difficulty unwinding and relaxing when you have time to yourself?					
15. How often do you find yourself talking too much when you are in social situations?					
16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
17. How often do you have difficulty waiting your turn in situations when turn taking is required?					
18. How often do you interrupt others when they are busy?					
Part B					



STEP 2: Look At Part A Results

If ≥4 'X' in SHADED ZONE, Screen is POSITIVE



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	Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
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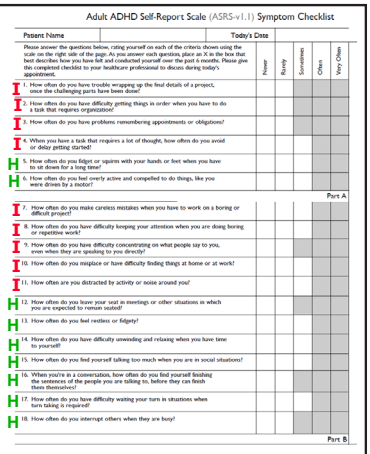
3. How often do you have problems remembering appointments or obligations?					
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?					
Part A					

STEP 3: If Screen +, Confirm 5 Hyperactive (H) and/or ≥5 Inattentive (I) Sx

Use Part A & Part B


Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name | Today's Date

Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.

		Never	Rarely	Sometimes	Often	Very Often
I	1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
I	2. How often do you have difficulty getting things in order when you have to do a task that requires organization?					
I	3. How often do you have problems remembering appointments or obligations?					
I	4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
H	5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
H	6. How often do you feel overly active and compelled to do things, like you were driven by a motor?					

Part A

I	7. How often do you make careless mistakes when you have to work on a boring or difficult project?					
I	8. How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
I	9. How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
I	10. How often do you misplace or have difficulty finding things at home or at work?					
I	11. How often are you distracted by activity or noise around you?					
H	12. How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
H	13. How often do you feel restless or fidgety?					
H	14. How often do you have difficulty unwinding and relaxing when you have time to yourself?					
H	15. How often do you find yourself talking too much when you are in social situations?					
H	16. When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
H	17. How often do you have difficulty waiting your turn in situations when turn taking is required?					
H	18. How often do you interrupt others when they are busy?					

Part B

DSM-5 Inattention (Need 5)

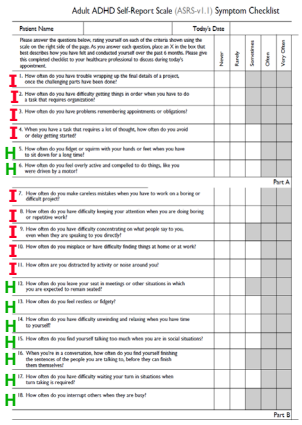
- Often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities
- Often has difficulty sustaining attention in tasks or activities that require sustained attention
- Often does not seem to listen
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
- Often loses things necessary for tasks or activities
- Is often easily distracted by extraneous stimuli
- Is often forgetful in daily activities

American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) American Psychiatric Association, Arlington 2013

DSM-5: Hyperactivity/Impulsivity (Need 5)

- Often fidgets with hands or feet or squirms in seat
- Often leaves seat in classroom or in other situations in which remaining seated is expected
- Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- Often has difficulty paying attention or engaging in leisure activities quietly
- Is often 'on the go' or often acts as if 'driven by a motor'
- Often talks excessively
- Often blurts out answers before questions have been completed
- Often has difficulty awaiting turn
- Often interrupts or intrudes on others (e.g., butts into conversations or games)

American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) American Psychiatric Association, Arlington 2013


Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

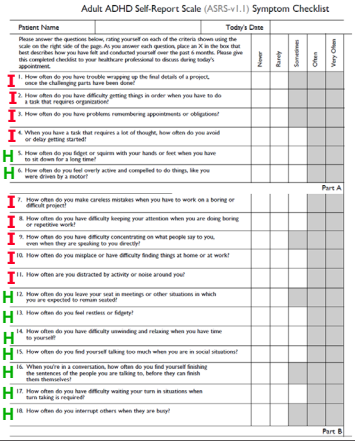
= DSM-5 Adjusted for Adults

DSM V Dx:

≥5 Inattentive

OR

≥5 Hyperactive/ Impulsive


Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

STEP 4: Review Scales A & B for IMPAIRMENTS

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist Instructions

Impairments

1) Review the entire Symptom Checklist & evaluate the level of impairment associated with the Sx
2) Confirm Sx began prior to age 12 years
3) Confirm ≥2 sites of impairment (work, school, social)
4) Ensure Sx not reflective of another disorder

\+ = Confirmed Dx ADHD

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist Instructions

Assess the presence of these Sx or similar Sx in childhood. Adults who have ADHD need not have been formally Dx in childhood*. In evaluating a patient's Hx, look for evidence of early-appearing and long-standing problems with attention or self-control. Some significant Sx should have been present in childhood, but full symptomology is not necessary.

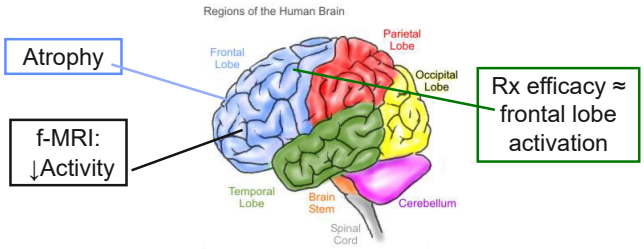
*emphasis added

For ADHD Dx, is Personal Recall Accurate?

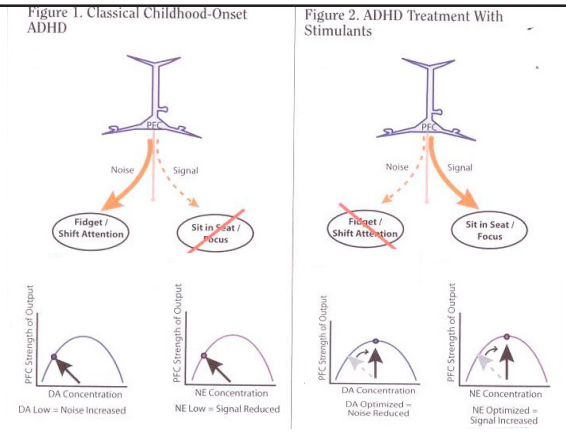
"Research shows that diagnosing ADHD based on the retrospective self-reports of adults is a valid method of diagnosing the disorder."

Wilens TE, Faraone SV, Biederman J "ADHD in Adults" *JAMA* 2004;292(5):619-623

ADHD Pathophysiology Links Rx



Higgins ES "Identifying and Treating adults with ADHD" *Patient Care* 2004;July:15-20



Stahl SM "MOA of Stimulants in ADHD" *J Clin Psychiatry* 2010;71(1):12-13

Adult ADHD Primary Treatments

Nonpharmacologic

CBT
Environmental Tools

Stimulants

Methylphenidate
Amphetamine

NERI

Atomoxetine

Central α_2 Agonists

Clonidine-ER, Guanfacine

Research

JAMA Psychiatry | Original Investigation

Association Between Medication Use for Attention-Deficit/ Hyperactivity Disorder and Risk of Motor Vehicle Crashes

Zheng Chang, PhD, MSc; Patrick D. Quinn, PhD; Kwan Hur, PhD; Robert D. Gibbons, PhD; Arvid Sjölander, PhD; Henrik Larsson, PhD; Brian M. D'Onofrio, PhD

JAMA Psychiatry 2017;74(6):597-603

ADHD Rx vs UnRx
Motor Vehicle Collisions (MVC)

- Study: US national cohort of ADHD subjects (n = 2,319,450) identified in commercial insurance claims data
- Method: 10 yr f/u comparing MVC in months on vs off Rx
- Results (when ON RX):
  - ♂: 38% lower MVC risk
  - ♀: 42% lower MVC risk

Chang Z et al *JAMA Psychiatry* 2017;74(6):597-603

ADHD Rx vs UnRx
Motor Vehicle Collisions (MVC)

Variable	Odds Ratio	
	Population Level	Intra-Individual
Men (MVC#)		
On vs Off Rx (2250 v 3151)	0.88 (0.84-0.93)	0.62 (0.56-0.67)
Women (MVC#)		
On vs Off Rx (2960 v 3134)	0.86 (0.820.90)	0.58 (0.53-0.62)

Chang Z et al *JAMA Psychiatry* 2017;74(6):597-603

MVC: ADHD Rx vs UnRx
Conclusions

"Among patients with ADHD, rates of MVCs were lower during periods when they received ADHD medication."

Chang Z et al *JAMA Psychiatry* 2017;74(6):597-603

MVC: ADHD Rx vs UnRx
Conclusions

"Considering the high prevalence of ADHD and its association with MVCs, these findings warrant attention to this prevalent and preventable case of mortality and morbidity."

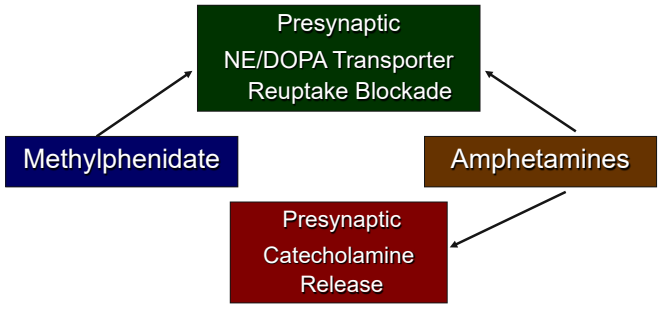
Chang Z et al *JAMA Psychiatry* 2017;74(6):597-603

ADHD Rx
Reduced Motor Vehicle Accidents

"Estimates of the population-attributable fraction suggested that up to 22.1% of the MVCs…could have been avoided if they had received medication during the entire follow-up"

Chang Z, Quinn PD, Hur K *JAMA Psychiatry* 2017;74(6):597-603

Extended-Release Stimulants: MOA



Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" J Clin Psychiatry 2011;72(7):1008-1014

Adult ADHD Rx: Extended-Release Stimulants*

- Dexmethylphenidate XR
- Mixed amphetamine salts
- Osmotic CR system (OROS) methylphenidate
- Lisdexamfetamine dimesylate

*shorter acting preparations not approved for adults

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" J Clin Psychiatry 2011;72(7):1008-1014

Stimulants: = efficacy

"Although methylphenidate is by far the most studied stimulant medication, the literature provides little evidence of differential response to the various available stimulants, although individual patients may respond preferentially."

Biederman J "A 55-YO Man with ADHD" *JAMA* 1998;280(12):1086-1092

XR Stimulants: Prescribing Points

- All comparably effective
- Start lowest dose and titrate
- Less abuse potential
  - OROS methylphenidate
  - Lisdexamfetamine
- Small ↑ BP & HR
  - Baseline EKG (+/-)
  - Monitor BP, pulse periodically

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

XR Stimulants: Adverse Effects

- Insomnia
- Abdominal Pain
- Anorexia
- Headache
- Dry Mouth
- Nausea
- Edginess
- BP/HR

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Will Stimulant Use PROMOTE Future Substance Use?

- Study Objective: assess risk for SUD associated with ADHD Rx
- Methods: ADHD Teens (≥ age 15) Rx with stimulants (n=56) vs UnRx ADHD (n=19) vs non-ADHD controls (n=137) followed X 4 years
- Outcomes: Relative risk for SUD at year 4

Biederman J, et al *Pediatrics* 1999;194(2):1-5

Will Stimulant Use PROMOTE Future Substance Use?

	UnRx ADHD vs Control	Rx ADHD vs UnRx
ANY SUD	6.3 (1.8-21.4)*	0.15 (0.04-0.6)*
Alcohol	5.8 (1.7-19.3)*	0.16 (0.05-0.57)*
Marijuana	3.1 (0.8-12.5)	0.42 (0.11-1.7)
Hallucinogen	1.0 (0.1-9.3)	0.76 (0.12-5.0)
Cocaine	7.5 (0.3-163.4)	0.2 (0.02-2.1)
Tobacco	0.85 (0.15-4.8)	2.4 (0.5-12.3)

*$p < 0.05$

Biederman J, et al *Pediatrics* 1999;194(2):1-5

Lisdexamfetamine Dimesylate (LDX)

- Long-acting prodrug (≥13 hrs)
- Indications
  - Children age 6-12
  - Adults
- Metabolism (primarily in bloodstream)
  - LDX→ l-lysine + d-amphetamine

Wigal T, Brams M, Gasior M, et al *Behavioral and Brain Functions* 2010;6(34):1-14

Wigal *et al. Behavioral and Brain Functions* 2010, 6:34
http://www.behavioralandbrainfunctions.com/content/6/1/34

BEHAVIORAL AND BRAIN FUNCTIONS

RESEARCH Open Access

Randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: novel findings using a simulated adult workplace environment design

Timothy Wigal*[1], Matthew Brams[2], Maria Gasior[3], Joseph Gao[4], Liza Squires[3], John Giblin[5] for 316 Study Group

Adult ADHD: LDX Rx

- Study: RDBPCT age 18-55 (n=104)
- Rx: LDX 30 mg, 50 mg, or 70 mg/d
- Major Exclusions
  - Comorbid psychiatric Dx
  - Suicide Risk
  - Recent substance abuse
  - BP >139/89
  - Seizures
  - Abnormal EKG

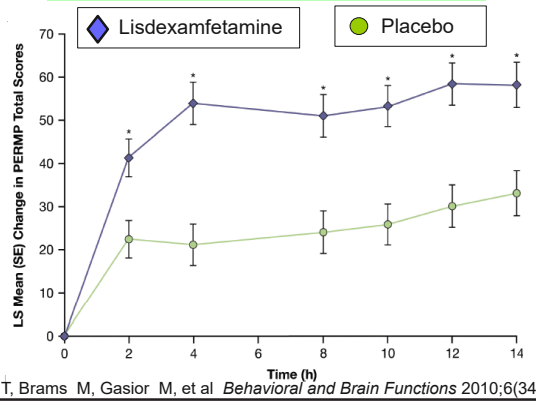
Wigal T, Brams M, Gasior M, et al *Behavioral and Brain Functions* 2010;6(34):1-14

Adult ADHD: LDX Rx
Study Setting: Simulated Adult Working Environment

- 2 sessions, 1 week apart
- Arrive 6:00 AM, depart 9:30 PM
- Scheduled class activities designed to provoke DSM-IV ADHD Sx
- Metrics (at AWE week 5 and 6 visits):
  - Permanent Product Measure of Performance (PERMP)
  - ADHD-RS-IV
  - CGI
  - AEs

Wigal T, Brams M, Gasior M, et al *Behavioral and Brain Functions* 2010;6(34):1-14

Lisdexamfetamine Effects on PERMP



Wigal T, Brams M, Gasior M, et al *Behavioral and Brain Functions* 2010;6(34):1-14

BRAIN RESEARCH 1381 (2011) 159–166

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Methylphenidate normalizes emotional processing in adult patients with attention-deficit/hyperactivity disorder: Preliminary findings

Annette Conzelmann[a], Eva Woidich[a], Ronald F. Mucha[a], Peter Weyers[a], Christian P. Jacob[b], Klaus-Peter Lesch[b,c], Paul Pauli[a,*]

[a]Department of Psychology, Biological Psychology, Clinical Psychology, and Psychotherapy, University of Würzburg, Germany
[b]Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Germany
[c]Molecular Psychiatry, Laboratory of Translational Neuroscience, University of Würzburg, Germany

ARTICLE INFO

Accepted 30 December 2010
Available online 6 January 2011

ABSTRACT

Emotional-motivational dysfunctions may significantly contribute to symptoms of attention-deficit/hyperactivity disorder (ADHD). Hyperactive-impulsive symptoms and sensation seeking could be the result of a search for reinforcers, and cognitive dysfunctions might be due to a low motivational drive. Emotional-motivational dysfunctions could also explain social dysfunctions in ADHD patients because they may

Methylphenidate & Emotional Processing: Results

"The data suggest that methylphenidate as first choice Rx in ADHD has a positive impact on emotional processes in adult ADHD patients and points to the clinical relevance of emotional dysfunctions in ADHD."

Conzelmann A et al *Brain Research* 2011:1381:159-166

Stimulant Rx Bottom Line Flexibilities

"In spite of pharmacologic and pharmacokinetic differences in stimulants…there do not appear to be differences in efficacy between short versus long-acting stimulants, or between amphetamines versus methylphenidate."

Bukstein O *UpToDate* 2018

Any Rationale for Atomoxetine or Antidepressants vs Stimulants?

The Flomax Vs Cardura Model

"In contrast to stimulants, which have a clinical effect almost immediately….atomoxetine and the antidepressants have a delayed onset of full therapeutic action of up to 4 weeks, related both to the titration…and the delay in the onset of action…."

Bukstein O *UpToDate* 2018

Stimulant Titration Process

- Start low dose in AM
- Titrate q1-4 weeks
- Titration Limits
  - Max improvement
  - Problematic AE's
  - Max Labeled dose

Bukstein O *UpToDate* 2018

Stimulants: What CV Effects Might Be Anticipated?

"CNS stimulants cause an increase in BP (mean ↑ approximately 2-4 mm HG) and heart rate (mean ↑ approximately 3-6 bpm)."

Quillivant (Methylphenidate HCl XR) 2012 FDA Prescribing Information

Stimulant CV Issues: What to Do?

- Screen for CV Sx PreRx
- Monitor BP/Pulse
  - Q1w initially
  - Q1-2 months long term

Bukstein O *UpToDate* 2018

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association.

ONLINE FIRST

ADHD Medications and Cardiovascular Risk

Some Heartening News

Philip Shaw, MD, PhD

JAMA 2011;306(24):2723-2724

Stimulants: CV Risk

"Few medications have received as much public scrutiny as those used for ADHD. The most serious concerns have centered on CV risk."

Shaw P *JAMA* 2011;306(24):2723-2724

Stimulants: CV Risk

"…this issue of JAMA compared approximately 150,000 adults prescribed ADHD medication with approximately 300,000 nonusers and found no evidence of a link between ADHD medication and MI, sudden cardiac death, or stroke."

Shaw P *JAMA* 2011;306(24):2723-2724

A-2 adrenergics in Adult ADHD: clonidine, guanfacine

"Little is known about [their] efficacy, safety, and tolerability….Small clinical trials have not shown these medications to reduce ADHD Sx in adults compared with placebo."

Bukstein O *UpToDate* 2018

NERI: Atomoxetine

- Nonstimulant
- Approved for adults & children
- Dopamine effects
  - thru NE transporters in prefrontal cortex
  - NOT in nucleus accumbens or striatum, ∴ not reinforcing

Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Atomoxetine: Adverse Effects

- Insomnia
- Anorexia (transient)
- Nausea (transient)
- Dry mouth
- ↓Libido
- ED
- ↑HR
- ↑BP

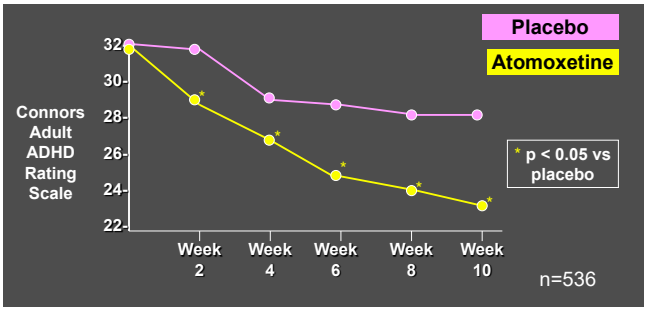
Adler LA et al "Optimizing Clinical Outcomes Across Domains of Life in Adolescents and Adults with ADHD" *J Clin Psychiatry* 2011;72(7):1008-1014

Adult ADHD: Atomoxetine v Placebo

- Study: 2 RPCTs adult ADHD (n=536)
- Rx: atomoxetine 120 mg/d (target)
  - mean dose = 92 mg/d
- Outcomes:
  - Connors Adult ADHD Rating Scale
  - ADHD Rating Scale
  - CGI-Severity Score

Michelson D, Adler L, Spencer T, et al "Atomoxetine in Adults with ADHD: Two RPC Studies" *Biol Psychiatry* 2003;53(20:112-120

Adult ADHD: Atomoxetine v Placebo



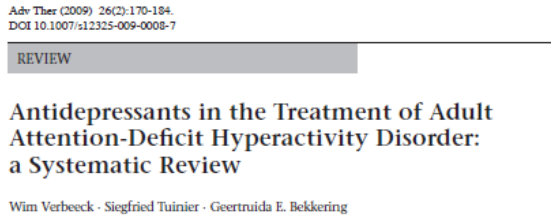
Michelson D, Adler L, Spencer T, et al "Atomoxetine in Adults with ADHD: Two RPC Studies" *Biol Psychiatry* 2003;53(20:112-120

Adult ADHD: Atomoxetine v Placebo AE's

Side Effect	Atomoxetine	Placebo
Dry Mouth	21%	7%
Insomnia	21%	9%
Nausea	12%	5%
↓Appetite	12%	5%
↓ Libido	7%	2%
ED	10%	1%
↑BP	1-3 mm Hg	-----
↑ Pulse	5 bpm	-----

Michelson D, Adler L, Spencer T, et al "Atomoxetine in Adults with ADHD: Two RPC Studies" *Biol Psychiatry* 2003;53(20:112-120

Stimulants Scare Me…Couldn't I Just Use Something Else?


Adv Ther (2009) 26(2):170-184.
DOI 10.1007/s12325-009-0008-7

REVIEW

Antidepressants in the Treatment of Adult Attention-Deficit Hyperactivity Disorder: a Systematic Review

Wim Verbeeck · Siegfried Tuinier · Geertruida E. Bekkering

Antidepressants for Adult ADHD? Systematic Review

- Source Material: 8 RCTs
  - Bupropion (5)
  - Lithium (1)
  - Paroxetine (1)
  - Desipramine (1)

Verbeeck W, Tuinier S, Bekkering GE "Antidepressants in the Rx of Adult ADHD: A Systematic Review" *Adv Ther* 2009;26(2):170-184

Why Bupropion?

- Mixed agonist of
  - dopamine
  - norepinephrine
- Previously used off-label
- Tmax = 2 hours, $T_{1/2}$ = 14 hours
- SR (b.i.d.) and XR (qd) formulations

Verbeeck W, Tuinier S, Bekkering GE "Antidepressants in the Rx of Adult ADHD: A Systematic Review" *Adv Ther* 2009;26(2):170-184

Adult ADHD Bupropion vs Placebo

- Study: RPCT adult ADHD (n=40)
- Rx: bupropion SR 200 mg b.i.d. X 6 weeks
- Clinical benefits not seen till weeks 5-6

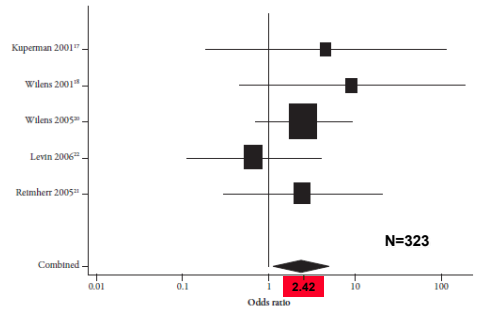
Verbeeck W, Tuinier S, Bekkering GE "Antidepressants in the Rx of Adult ADHD: A Systematic Review" *Adv Ther* 2009;26(2):170-184

Adult ADHD Bupropion vs Placebo

	Bupropion	Placebo
CGI-I much-very much improved	52%	11%
ADHD-RS Improvements	76%	37%

Verbeeck W, Tuinier S, Bekkering GE "Antidepressants in the Rx of Adult ADHD: A Systematic Review "*Adv Ther* 2009;26(2):170-184

Adult ADHD Bupropion vs Placebo: Meta-Analysis



Verbeeck W, Tuinier S, Bekkering GE "Antidepressants in the Rx of Adult ADHD: A Systematic Review" *Adv Ther* 2009;26(2):170-184

Adult ADHD Other Agents Desipramine

- Study: RPCT Adult outpatients (n=41)
- Rx: desipramine (mean 147 mg/d) v placebo
- Outcome: "Improved"
  - CGI-I score 1-2 (much/very much improved) AND
  - Adult ADHD-RS reduction ≥30%
- Results (% improved):
  - Desipramine = 68%
  - Placebo = 0%
- Improvements noted by week 2 and progress

Verbeeck W, Tuinier S, Bekkering GE "Antidepressants in the Rx of Adult ADHD: A Systematic Review" *Adv Ther* 2009;26(2):170-184

Adult ADHD Other Agents Paroxetine: maybe NOT

N=98 20 weeks Rx	CGI Response
Placebo	16%
Paroxetine	17%
Paroxetine + Dextroamphetamine	44%
Dextroamphetamine	64%

Verbeeck W, Tuinier S, Bekkering GE "Antidepressants in the Rx of Adult ADHD: A Systematic Review" *Adv Ther* 2009;26(2):170-184

So……

Which ADHD Rx is BEST?

A Comparison of the Efficacy of Medications for Adult ADHD Using Meta-Analysis of Effect Sizes

Stephen V. Faraone, PhD, and Stephen J. Glatt, PhD

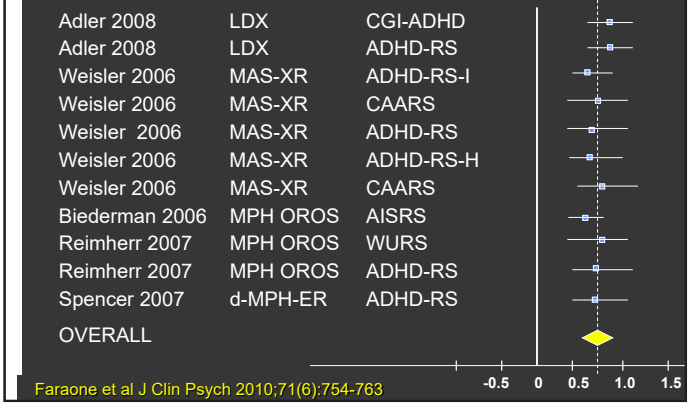
J Clin Psychiatry 2010;71(6):754-763

Adult ADHD Rx Meta-Analysis Meds Reviewed

- Atomoxetine
- Bupropion SR, XL
- Modafinil
- Paroxetine
- Mixed Amphetamine Salts IR, XR
- Dextroamphetamine
- Methylphenidate IR, OROS
- Dexmethylphenidate ER
- Lisdexamphetamine

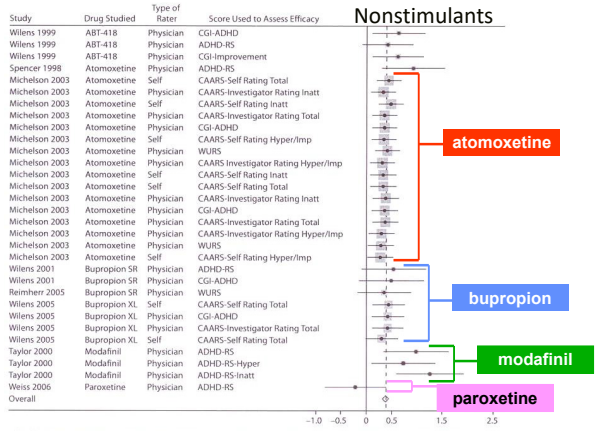
Faraone SV, Glatt SJ *J Clin Psych* 2010;71(6):754-763

Long-Acting Stimulants



Faraone et al J Clin Psych 2010;71(6):754-763

Nonstimulants



Faraone et al *J Clin Psych* 2010;71(6):754-763

Stimulants vs Non-Stimulants It's a Matter of TIME & EFFECT

"In contrast to stimulants, which have a clinical effect almost immediately… atomoxetine and the antidepressants have a delayed onset of full therapeutic action of up to four weeks…."

Bukstein O *UpToDate* accessed 018-May-8

Goals

- Develop conviction that adult ADHD is a legitimate clinical entity
- Engender interest in identifying adult ADHD more often because of its compelling epidemiologic presence, consequences, and comorbidities
- Enhance confidence in the role of primary care clinicians to Dx and Rx adult ADHD
- Confirm concrete outcomes benefits from Rx

SELF EVALUATION

Identifying and Treating ADHD

1. Some clinicians are skeptical about the legitimacy of ADHD as a medical disorder. The perspective of the WHO (World Health Organizatio on ADHD is

    a. Except for the United States, ADHD has little consequence
    b. Except for the United States and western Europe, ADHD has little consequence
    c. ADHD has worldwide adverse consequence

2. Which of the following is not a DSM5 criterion for ADHD diagnosis?

    a. Onset prior to age 6
    b. At least 5 symptoms of hyperactivity or inattention
    c. Impact in at least 2 sectors of life (e.g., work, schoo
    d. Symptoms not explained by another disorder (e.g., bipola

3. ADHD is associated with multiple different adverse social manifestations, some of which appear to be related to excessive risk taking and/or impulsivity. Which consequences below are substantiated in the literature?

    a. > 4 fold increase in STI
    b. > 10 fold increase in teen pregnancy
    c. >2 fold increase in multiple MVA's
    d. All of the above

4. Both stimulants (e.g., methylphenidate, amphetamine salt and non-stimulants e.g., atomoxetin are effective ADHD treatments. Which statement is correct?

    a. The effect size of atomoxetine is greater than stimulants
    b. The effect size of stimulants is greater than atomoxetine
    c. Atomoxetine does not cause insomnia
    d. The onset of efficacy of atomoxetine is more rapid than stimulants

5. According to an article published in JAMA on adult ADHD, "…approximately___of adults with substance abuse disorders, anxiety, depressive disorders, and bipolar disorders have ADHD."

    a. 1-2%
    b. 5-10%
    c. 15-20%
    d. 25-30%

Answer Key: 1. C, 2. A, 3. D, 4. B, 5. C

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Carole C. Foos, CPA, is a partner in OJM Group, a physician focused financial planning and asset management firm and a Certified Public Accountant (CPA) offering tax analysis and tax planning services to the firm's clients. Ms. Foos has over 25 years of experience in accounting, tax planning and financial consulting. She is a co-author of numerous books for physicians, including *Wealth Management Made Simple* and *Wealth Planning for the Modern Physician: Residency to Retirement*. Ms. Foos has authored numerous articles and presented many lectures, webcasts, and podcasts on tax planning and wealth management.

You may contact Ms. Foos with any questions or comments at (513) 309–3946 or by email at carole@ojmgroup.com.

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Healthcare Practice Financial Literacy – Parts 1 & 2

Carole C. Foos, CPA

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- Text **AEIOJM** to 844-418-1212
  - Click the link in the reply text
- Visit ojmbookstore.com and enter **AEIOJM** at checkout
- Scan the QR Code

LEARNING OBJECTIVE:

GAIN A BETTER UNDERSTANDING OF BUILDING WEALTH UTILIZING:

- TAX PLANNING
- ASSET PROTECTION
- INVESTMENT PLANNING
- AVOIDING FINANCIAL PITFALLS

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ASSET PROTECTION

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TYPES OF LIABILITY FACING PHYSICIANS & DENTISTS

- Medical/dental malpractice
- Employer liability
  - Sexual harassment ("hostile work environment"); Wrongful termination (protected classes); Violation of fiduciary duty (qualified plans)
- Billing issues
  - Over-billing, improper billing, fraud, violation of anti-kickback rules, Stark rules, etc.
- HIPAA
- Premises liability
- Personal liability

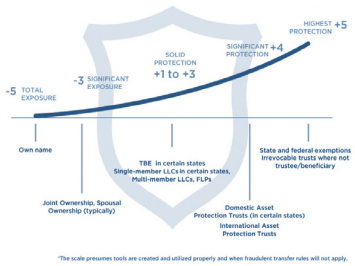
ASSET PROTECTION FITNESS

Your ability to earn an income may be your greatest asset. Make sure you are well protected against other risks.

- **Protection objectives: Discouragement, Settlement, Protection**
- Insurances:
  - P&C: practice: all coverages, renewed focus on business interruption? Cyber?
  - Disability: your greatest asset is often the ability to work
  - Life insurance: death benefit for family, cash value insurances have investment floors
  - **Whole life policies will credit dividends of 5-6%, Equity-indexed will have floor of 0%**
- Asset protection:
  - Review by an expert
  - Proper ownership structure
  - Proper language in operating agreements
- Estate planning: for yourselves and parents

BEST ASSET PROTECTION NOT AP

- Why wealth protection MUST be tied to wealth creation: timing
  - Fraudulent transfer law
  - Transfer for less then fair value that leaves one unable to pay debt
- Insurance is a key component
  - Commercial/personal, captives, RRGs
- AP must be implemented in a multidisciplinary approach
  - Legal, Financial, Insurance
- Legal planning - like tax planning: economic substance
- Top (+5) tools are primarily not AP tools



*The scale presumes tools are created and utilized properly and when fraudulent transfer rules will not apply.

INSURANCES AS FRONT-LINE PROTECTORS

- Types of policies
  - Medical or dental malpractice
  - General Liability
  - Cyber
  - Landlord
  - Other
- Be aware of coverage limitations, deductibles
- Review and get second opinions

CHOICE OF ENTITY FOR NON-PRACTICE BUSINESSES

	Corporation	LLC
Inside Protection	Yes. General corporate law principles.	Yes. General corporate law principles.
Outside Protection	**None, unless licensure for professional corporations.**	Charging order protections available. (+2)

PROTECTING EQUIPMENT & REAL ESTATE

MAXIMIZE PROTECTIVE BENEFIT PLANS

- **Shields #1 asset – cash flow**
- Qualified retirement plans (QRPs): state exemption laws vary
  - Most states also protect QRPs to an unlimited value
  - Some states: value limitations
  - Some states: timing claw-backs
- Non-qualified plans – depends on funding mechanism
  - COLI – about 20 states provide (+5) exemption
  - Other states: can use trusts or LLCs

TITLING ASSETS: DOES IT PROTECT?

- Spousal
- Basics: Tenancy in common, joint tenancy
- Tenancy by the Entirety (TBE)
- Community Property

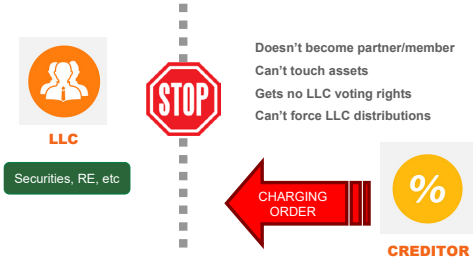
START WITH EXEMPT ASSETS (+5)

- (+5) Federal or state exempt asset
- No gifting, compliance, accounting fees or special taxes
- Protection cannot be matched by any other planning
- Federal bankruptcy exemptions for QRPs and IRAs
- States vary widely
  - Homestead
  - QRPs, IRAs
  - Life insurance and annuities

LLCs (+2): IDEAL FOR MOST ASSETS BEYOND EXEMPTIONS

- Inside Creditors
- Outside Creditors Isolates their lawsuit damage only to LLC property
  - Creditors can only get "charging order" against the LLC interest (+1 to +3) depending on use, compliance
  - Should tie into your estate plan
- "Building blocks" of asset protection
- *Control and Access*

WHAT A "CHARGING ORDER" MEANS



KEYS TO PROTECTION: LLCs

- Proper operating agreement
- Compliance with annual formalities
- Non-asset protection purpose: estate planning/gifting
- Jurisdiction: use the best state, when you have options
- Many LLCs are lacking in 1 of the 4 elements above: vulnerable
- Key: experienced attorney who has annual monitoring/gifting plan

PROTECTING THE HOME

- Homestead protection is best
- Tenancy by the entirety (TBE) in those states that protect TBE well
- Next best option:
  - Usually debt shield

WEALTH PLANNING

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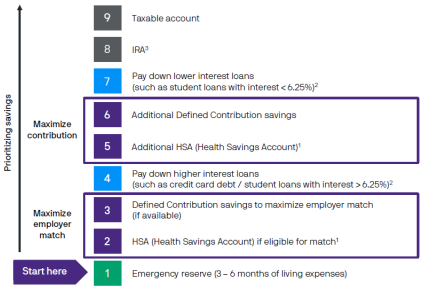
FOCUS ON WEALTH ACCUMULATION

"It's not how much money you make, but how much money you keep, how hard it works for you, and how many generations you keep it for."

Robert Kiyosaki

SAVINGS HIERARCHY



RETIREMENT SAVINGS CHECKPOINT

Current age	Current household income: $30,000	$40,000	$50,000	$60,000	$70,000	$80,000	$90,000
	Checkpoint (x current household income)						
25	See "Annual savings needed" on slide 16"	0.1	0.1	0.3	0.5	0.6	0.8
30		0.2	0.5	0.7	1.0	1.1	1.3
35		0.6	0.9	1.1	1.5	1.7	1.9
40		0.3	1.1	1.4	1.7	2.2	2.4	2.6
45		0.7	1.6	2.1	2.4	3.0	3.2	3.5
50		1.1	2.3	2.8	3.2	3.9	4.1	4.5
55		1.7	3.0	3.6	4.1	4.8	5.2	5.6
60		2.2	3.7	4.4	4.9	5.8	6.1	6.7
65		2.5	4.1	4.9	5.5	6.5	6.9	7.5

Current age	Current household income: $100,000	$125,000	$150,000	$175,000	$200,000	$250,000	$300,000
	Checkpoint (x current household income)						
25	0.1	0.3	0.5	0.7	0.8	1.0	1.2
30	0.6	1.0	1.2	1.5	1.6	1.9	2.1
35	1.5	1.9	2.2	2.5	2.7	2.9	3.2
40	2.5	3.0	3.3	3.7	3.9	4.2	4.6
45	3.6	4.3	4.7	5.1	5.4	5.8	6.2
50	5.0	5.8	6.3	6.7	7.1	7.6	8.0
55	6.5	7.5	8.0	8.5	8.9	9.5	10.0
60	8.0	9.1	9.7	10.3	10.8	11.4	12.0
65	9.3	10.5	11.1	11.8	12.3	13.0	13.7

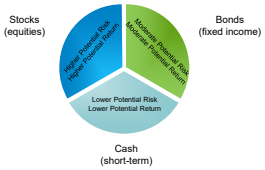
This analysis assumes you would like to maintain an equivalent lifestyle in retirement. Household income is assumed to be gross income (before taxes and savings).

How to use:

- Go to the intersection of your current age and your closest current household income.
- Multiply your current household income by the checkpoint shown. This is the amount you should have saved today, assuming you continue contributions of 5% going forward.
- **Example: For a 40-year-old with a household income of $50,000: $50,000 x 1.4 = $70,000**

THE PRINCIPLES OF ASSET ALLOCATION

Asset allocation = combining different investment types



*** Up to 91.5% of variations in returns can be attributed to asset allocation**

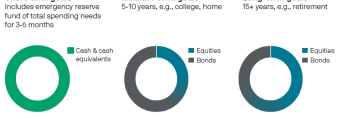
* Source: "Determinants of Portfolio Performance," Brinson, Hood and Beebower, *Financial Analysts Journal*, July-August 1986, and "Determinants of Performance II: An Update," Brinson, Singer and Beebower, *Financial Analysts Journal*, May-June 1991. This represents a landmark study which has not been refuted and which stands today as a valid, widely accepted theory.

GOALS BASED WEALTH MANAGEMENT

Short-term goals
Includes emergency reserve fund of total spending needs for 3-6 months

Medium-term goals
5-10 years, e.g., college, home

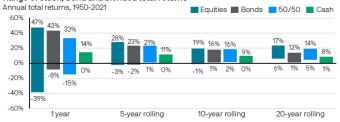
Long-term goals
15+ years, e.g., retirement



Divide and conquer

Aligning your investment strategy by goal can help you take different levels of risk based on varying time horizons and make sure you are saving enough to accomplish all of your goals – not just the ones that occur first.

Range of stock, bond and blended total returns
Annual total returns, 1950-2021



Source (top chart): J.P. Morgan Asset Management.
Source (bottom chart): Bloomberg, FactSet, Federal Reserve, Robert Shiller, Strategas/Ibbotson, J.P. Morgan Asset Management.
Returns shown are based on calendar year returns from 1950 to 2021. Stocks represent the S&P 500 Shiller Composite and Bonds represent Strategas/Ibbotson for periods from 1950 to 2010 and the Bloomberg Aggregate thereafter. Cash represents the U.S. 90-Day Treasury Bill Total Return.
Portfolio allocations are hypothetical and are for illustrative purposes only. They were created to illustrate different risk/return profiles and are not meant to represent actual asset allocation.

7 QUESTIONS TO ASK YOUR ADVISOR / PROSPECTIVE ADVISOR

1. Does your advisor owe you a fiduciary duty as a client, or are they held only to a "suitability" standard?
2. Can your advisor provide a detailed explanation of all the ways in which they are compensated?
3. Does your advisor's firm make money in other ways on your individual investments?
4. Does your advisor use an outside custodian?
5. Does your advisor utilize proprietary securities?
6. Does the advisor's firm engage in investment banking activities?
7. How does the advisor communicate with you and how often?

FIDUCIARY VS SUITABILITY

- A fiduciary advisor has a ***fiduciary*** duty to his or her clients, which means that he or she has a fundamental obligation to provide suitable investment advice and ***always act in the clients' best interests.***
- A broker ***does not need to act in the best interests of the underlying customer.*** Instead, their actions must only be ***suitable*** for the client.
- A key distinction in terms of loyalty is also important, in that ***a broker's duty is to the broker-dealer he or she works for***, not necessarily the client served.
- **#1 mistake made by physician investors: not using a fiduciary when getting professional investment advice.**

HOW TO RECOGNIZE THE TYPE OF FIRM YOU WORK WITH

ADVISOR
Fiduciary
Advice Driven
Transparency
Registered Investment Advisor
3rd Party Custody
No Proprietary Products

VS

BROKER
Suitability
Transaction Based
Disclosure
Investment or Financial Advisor
In-house Custody
Proprietary Products

FIDUCIARY VS SUITABILITY: STOCK FUND PURCHASE EXAMPLE

- Client A contacts his broker and expresses an interest in investing $50,000 in U.S. growth stocks. The broker invests the client assets in Fund XYZ, which charges a sales load of 5.75 percent with operating expenses of 0.68 percent annually. The client will immediately pay a one-time fee of $2875 on the trade on top of the recurring fund–management fee. In this case, the suitability standard has been met.
- Client B contacts his Registered Investment Advisor, a fiduciary firm, with the same request. The investment advisor purchases an ETF with a gross expense ratio of 0.18 percent and pays a commission of $8.95 on the trade. This client pays his RIA a management fee of 1 percent of the assets, which equates to $500 per year on $50,000. The advisor has met the fiduciary standard.
- **In our very realistic example, the front-loaded fees paid by client A are significant enough that it would require a commitment of approximately nine years to this fund family before that commission is equal to the sum of advisory fees paid by client B.**

SEQUENCE OF RETURNS RISK

SEQUENCE OF RETURNS RISK

Hypothetical example

	PORTFOLIO A		PORTFOLIO B	
Year	Return	Balance	Return	Balance
0		$100,000		$100,000
1	–15%	$80,750	22%	$115,900
2	–4%	$72,720	8%	$119,772
3	–10%	$60,948	30%	$149,204
4	8%	$60,424	7%	$154,298
5	12%	$62,075	18%	$176,171
6	10%	$62,782	9%	$186,577
7	–7%	$53,737	28%	$232,418
8	4%	$50,687	14%	$255,257
9	–12%	$40,204	–9%	$231,374
10	13%	$39,781	16%	$262,594
11	7%	$37,216	–6%	$242,138
12	–10%	$28,994	17%	$277,452
13	19%	$28,553	19%	$324,217
14	17%	$27,557	–10%	$287,296
15	–6%	$21,204	7%	$302,056
16	16%	$18,796	13%	$335,674
17	–9%	$12,355	–12%	$290,993
18	14%	$8,612	4%	$297,433
19	28%	$4,624	–7%	$271,962
20	9%	$0	10%	$293,658
21	18%	$0	12%	$323,297
22	7%	$0	8%	$343,761
23	30%	$0	–10%	$304,885
24	8%	$0	–4%	$287,890
25	22%	$0	–15%	$240,456
Arithmetic Mean	6.8%		6.8%	
Standard Deviation	12.8%		12.8%	
Compound Growth Rate	6%		6%	

TECHNIQUES TO REDUCE YOUR INVESTMENT TAX BILL

- Take advantage of account registration
  - Active funds & bonds in deferred accounts, ETFs in taxable
- Own municipal bonds in taxable accounts
  - Tax free rates vs. ordinary income, understand breakeven points
- Be aware of holding periods
  - 23.8% vs 40.8% LT vs. ST Cap gains
- Offset gains by realizing losses
  - Diversify across asset classes to create planning opportunity
  - Real example: $3 mil client, 194k gains, 50k realized, offset 30k with swap, savings $7,140
- Think twice about gifting cash
  - Gifting appreciated stock can make your contribution worth 20% more
- Understand your fund's tax cost ratio
  - Annualized return reduced by tax on income / distributions

30

TAX PLANNING

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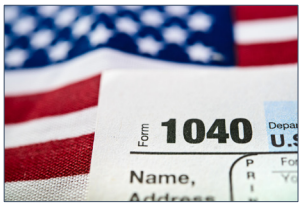
PLANNING FOR THE FUTURE OF UNKNOWN TAX RATES

- Understanding your retirement plan and how it will be taxed
  - Taking advantage of employer contributions
  - Qualified vs. non-qualified plans
  - Tax rates in earning years vs. in retirement years
- Savings outside of your retirement plan
  - Importance of tax efficient investing
  - Dividend and capital gains rates
- Building wealth through tax diversification
  - The three buckets
- Protecting your estate for your heirs
  - Ever changing estate tax exemption



TAX DIVERSIFICATION

ORDINARY INCOME	CAPITAL GAINS	TAX FREE
37.0% FEDERAL + 6.6% STATE + 3.8% ACA	20% FEDERAL + 6.6% STATE + 3.8% ACA	
(47.4% TAX)	(30.4% TAX)	(0% TAX)
WITHDRAWAL: $100,000	WITHDRAWAL: $100,000	WITHDRAWAL: $100,000
LESS TAX: $47,400	LESS TAX: $30,400	LESS TAX: $0
NET AFTER TAX: $52,600	NET AFTER TAX: $69,600	NET AFTER TAX: $100,000

TAX DIVERSIFICATION

- Many physicians have high concentration of retirement assets in qualified plans
  - Traditional plans offer deductible contributions and tax deferred growth
  - Distributions from these plans will be taxed at ordinary income tax rates in effect at time of distribution
- Physicians often have low concentration of assets that will be taxed at capital gains rates or that will be tax free
- Hedging against future tax rate changes is desirable
- Back door Roth has been one way to hedge

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ANOTHER WAY TO FILL THE TAX-FREE BUCKET

Utilize permanent life insurance policy to supplement retirement income:

- Premiums are paid with after tax dollars
- Premiums cover the cost of death benefit as well as building cash value in the policy
- Cash value can be invested in various types of investments, depending on the policy
  - Investment options often contain a floor which provides downside protection
  - They also contain a cap
- Owner can borrow against the cash value, generally tax free
- Policy design, interest rate on borrowing and insured's health are key

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RETIREMENT PLANS

- QRP contributions are tax deductible (401(k)s, profit sharing plans, DB plans, SEP IRAs)
- Contributions grow tax deferred but are taxed at ordinary income tax rates as distributed
- **SO… if a different type of plan or design allows for greater deductions, or more efficient for owners or lower cost, look into adopting now for 2023**
- *Beyond the deduction for the QRP contribution, for some owners in practices taxed as pass through entities, there can be a 2nd level of deduction created under 199A if the QRP contribution lowered the owner's personal taxable income below thresholds for SSTBs.*

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QRP'S: DEFINED CONTRIBUTION PLANS AND SEP IRA'S

- IRS defines the contribution amount
- 401(k)s, 403(b), and 457 plans
  - $22,500 employee deferral amount
  - $30,000 with catch up
- PS: Defined contribution maximum $66,000
- Flexibility on funding
  - No penalties for underfunding or termination
- **Proper plan design is key**

CASH BALANCE PLANS

- Tax Reform has provided additional opportunities – bringing taxable income down below threshold so 20% QBI deduction is not phased out for professionals
- ***Tax Benefits*** - Contributions to the Plan are Tax Deductible and investment return is tax deferred.
- ***Higher*** tax-deductible ***contributions*** than 401(k) alone – use in combination
- Creditor Protection
- Increase retirement benefits for employees *(paid for by tax benefits to owners)*
- Can include death benefits funded with life insurance in addition to retirement benefits (also a way to fund tax free retirement income)
- Can include 401(h) for tax free Retiree Medical expenses

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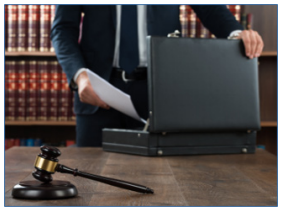
NON-QUALIFIED PLANS

- Non-qualified plans – asset protection depends on plan/state
- Significant other benefits:
  - Present tax deductions – maybe but generally not
  - Long term tax growth deferred and can be designed so that distributions are tax free
  - Discrimination is permitted
  - Reward / retain key employees
  - Save more for retirement to meet goals



39

ROTH PLANS

- Contributions of after-tax dollars
  - Taxed at your current rate
- Tax free growth
  - Assuming funds stay in at least 5 years from time Roth started
- Distributions tax free
  - No required minimum distributions
- Over income limit for Roth IRA contribution but not for Roth 401(k)
  - Salary deferral to Roth / profit sharing or match to traditional or Roth
  - No income limit for Roth conversions currently

40

CORPORATE STRUCTURE

- Sole Proprietorship / Single Member LLC
- Multiple Member LLC
  - Partnership
  - C Corporation
  - S Corporation
- Partnership
  - General Partnership
  - Limited Partnership
- Corporation
  - C Corporation
  - S Corporation
- Consider multiple entity structure for tax planning and asset protection

CORPORATE STRUCTURE

- Correct choice of entity
  - May be able to change
- Asset Protection considerations
- Utilize the entity choice correctly with the right compensation structure and profit distribution structure
  - Partnership – income vs guaranteed payment
  - S corporation – don't be taxed like a C Corp
    - BBB Act could change this
  - C corp – double tax conundrum
  - Sole proprietorship – Medicare tax on all net income
  - Health insurance for partners and S Corp shareholders
- QBI deduction – managing the threshold

SECTION 199A QBI

There will be a 20% deduction against **QUALIFIED BUSINESS INCOME (QBI)** of pass-through entities *(S corps, partnerships, LLC's, sole proprietorships, trusts, estates)*

- Effective 2018 through 12/31/2025
- Deduction amount will be the lesser of:
  - 20% of the taxpayer's qualified business income; or
  - 20% of taxable income less net capital gains
- For **business owners below the applicable threshold *amount*** *($182,100 single / $364,200 joint)* there are no further limitations
  - Owners of any non-corporate business in any industry qualify if under the threshold
  - No W-2 limitation if under the threshold
  - Partial deduction if TI below $232,100 / $464,200
- Effectively reduces tax rate on QBI from 37% to 29.6%
- **Can you get yourself below the threshold with QRP deduction or additional changes???**
  - Increase retirement contributions
  - Transfer ownership
  - Corporate structure changes

FINANCIAL PITFALLS

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TAX PITFALLS

- Lack of diversification
- Failure to take advantage of corporate structure
- Inability to maximize and diversify retirement plans
- Lack of planning during earning years

ASSET PROTECTION PITFALLS

- Poor insurance coverage
- Not utilizing +5 assets
- Poor titling of assets
- Lack of strong operating agreements

WEALTH PLANNING PITFALLS

- Failure to use goals-based planning
- Too much risk in portfolio as withdrawals begin
- High tax drag on investments
- Failure to properly allocate assets and match your risk tolerance
- Failure to understand how advisor is paid

PERSONAL WEALTH PLANNING

DIAGNOSTIC vs. TREATMENT

ADVICE & EXPERTISE FOR A FLAT FEE

BUILDING A RELATIONSHIP

OJMGROUP

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SELF EVALUATION

Healthcare Practice Financial Literacy – Parts 1 & 2

1. T/F - A qualified retirement plan offers the highest level of asset protection (+5).

2. T/F - Titling all my valuable assets in my spouse's name protects me if my spouse is involved in a car accident.

3. An LLC offers excellent asset protection since charging orders for creditors allow them to

a. Get LLC voting rights
b. Limit their lawsuit damages to LLC property only
c. Force LLC distributions
d. Become a partner / member

4. T/F - The first step to starting a savings plan is a 3-6 month emergency reserve of living expenses.

5. T/F - An advisor who has a fiduciary duty to his clients must always do what is in the client's best interest.

6. Having the same average annual return in 2 separate portfolios of retirees withdrawing assets where one runs out of money and the other does not is called

a. Indexing
b. Harvesting capital losses
c. Sequence of Returns Risk
d. Suitability standard

7. One way to reduce your investment tax bill is to

a. Hold assets at least 12 months prior to selling
b. Own municipal bonds in taxable accounts
c. Gift appreciated stock instead of cash to charity
d. All of the above

8. T/F - Tax diversification means having assets in each of 3 income buckets: ordinary income, capital gains and tax-free.

9. Utilizing permanent life insurance as a way to supplement retirement income helps to fill which bucket?

a. Ordinary income
b. Capital gain
c. Tax free
d. None of the above

10. The maximum that an employee under age 50 can defer from his or her salary into a 401k plan in 2023 is:

a. $19,500
b. $22,500
c. $30,000
d. $66,000

11. T/F - The asset protection features of a non-qualified retirement plan is the same in every state.

12. T/F - The earnings growth on a Roth 401k account or a Roth IRA account is tax free as long as the account has been open for at least 3 years prior to taking withdrawals.

13. Which of the following corporate structures has the potential for double taxation?

a. Partnership
b. Sole proprietorship
c. S corporation
d. C corporation

14. T/F - Cash balance plans generally offer higher tax-deductible contributions than 401k plans alone.

Answer Key: 1. T, 2. F, 3. B, 4. T, 5. T, 6. C, 7. D, 8. T, 9. C, 10. B, 11. F, 12. F, 13. D, 14. T

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Obesity: Primary Care Management

Obesity: Primary Care Management Agenda

- Classification & Epidemiology
- Pathophysiology
- Pharmacotherapy
- Non-pharmacologic Therapy

Almost 30 Years Later: Are Things Any Different?

"These are uncertain times for obese persons and those who seek to help them."

Foster GD, Kendall PC. "The Realistic Treatment of Obesity: Changing the Scales of Success" Clinical Psychology Review 1994;14(8):701-736

A Classification of Obesity

Body Mass Index (BMI) kg/m^2

- 25-29.9 = Overweight
- 30-34.9 = Obese (Class I)
- 35-39.9 = Moderate Obesity (Class II)
- 40-49.9 = Morbid Obesity (Class III)
- >50 = Super Morbid Obesity (Class IV)

It's Best To MEASURE Height & Weight
Obesity: Limitations of Self-Reported Data

- overweight participants underestimate weight
- all participants overestimate their height
  - ∴ true obesity rates underestimated

Mokdad AH, et al. *JAMA*;1999; 282:1519-1522

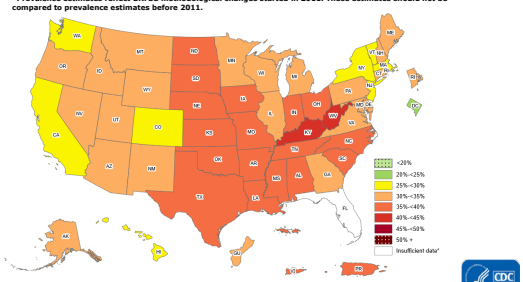
BMI: SOME EXCEPTIONS

- Body Builders
- Pregnancy/Lactation
- Ascites
- CHF
- Amputees
- Peripheral Edema
- TZDs

Why Bother? Epidemiology

Prevalence[1] of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2021

[1] Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



*Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

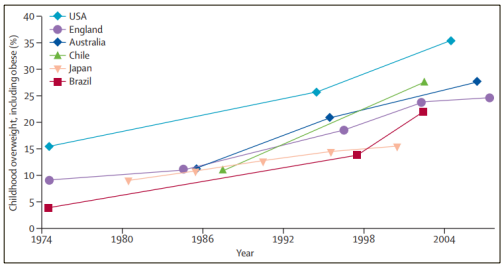
Obesity Prevalence: Now vs Then

ADULTS	
1999-2000	2019-2020
30.5%	41.9%

YOUNG ADULTS	
1976-1980	2017-2018
6.2%	33%

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Obesity in the USA: We Are Not Alone



Swinburn BA, et al. Lancet 2011;378:804-14

Why Bother? Consequences

Consequences of Obesity

- 25 y.o. morbidly obese male (BMI >40) compared to a 25 y.o. old man (BMI 24):
  - 22% reduction in lifespan
  - loss of 12 years of life

Fontaine, et. al. Years of life lost due to obesity. *JAMA* 2003;289:187-193

BENEFITS of WEIGHT LOSS

Obesity Rx: Reason for Hope?

"Weight reduction as little as 5% in obese patients is associated with an improvement in the CV risk profile, a ↓ in the incidence of DM, and the reduction of pain associated with osteoarthritis."

Fidler MC et al *J Clin Endocrinol Metab* 2011;96:3067-3077

Does *Intentional* Weight Loss Improve Outcomes?

CANCER PREVENTION STUDY 1

- Adults (age 40-60) recruited Oct 1959-March 1960
- n=1,078,894
- Intake Health Questionnaire 8 X (thru 1972)
- Analysis limited to women BMI >27 (n = 88,760)
- Never-smokers only
- Outcomes: only women who *intentionally* lost weight

Williamson D *Am J Epidemiol* 1995;141:1128-1141

Does Weight Loss Improve Outcomes? Results in Women Losing ≥20#

- All cause mortality: ↓20%
- Obesity-related CA mortality: ↓40-50%
- Diabetes-associated mortality: ↓30-40%

Williamson D *Am J Epidemiol* 1995; 141 :1128-1141

Pathophysiology

It's NOT Simple Thermodynamics

I'm Overweight Because I Chose My Parents Poorly

I Am Overweight Because My Parents Were

The New England Journal of Medicine

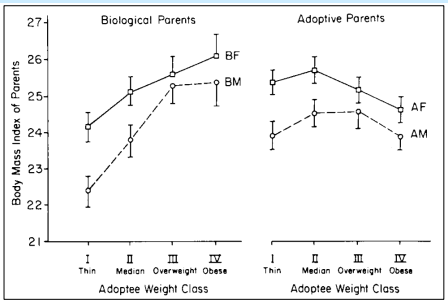
Volume 314 JANUARY 23, 1986 Number 4

AN ADOPTION STUDY OF HUMAN OBESITY

ALBERT J. STUNKARD, M.D., THORKILD I.A. SØRENSEN, DR.MED., CRAIG HANIS, PH.D., THOMAS W. TEASDALE, M.A., RANAJIT CHAKRABORTY, PH.D., WILLIAM J. SCHULL, PH.D., AND FINI SCHULSINGER, DR.MED.

Abstract We examined the contributions of genetic factors and the family environment to human fatness in a sample of 540 adult Danish adoptees who were selected from a population of 3580 and divided into four weight classes: thin, median weight, overweight, and obese. There was a strong relation between the weight class of the adoptees and the body-mass index of their biologic parents — for the mothers, $P<0.0001$; for the fathers, $P<0.02$. There was no relation between the weight class of the adoptees and the body-mass index of their adoptive parents. Cumulative distributions of the body-mass index of parents showed similar results; there was a strong relation between the body-mass index of biologic parents and adoptee weight class and no relation between the index of adoptive parents and adoptee weight class. Furthermore, the relation between biologic parents and adoptees was not confined to the obesity weight class, but was present across the whole range of body fatness — from very thin to very fat. We conclude that genetic influences have an important role in determining human fatness in adults, whereas the family environment alone has no apparent effect. (N Engl J Med 1986; 314:193-8.)

Obesity: Nature Trumps Nurture



Stunkard AJ, et al *NEJM* 1986;314(4):193-198

I'm Overweight Because I Caught A Virus

I Am Overweight Because I Caught A Virus

History

- Early 1990's Bombay, India:
  - Adenovirus #36 infects chicks → unexpected weight gain
- 1996 : chicks injected with ad-#36 become fat within 3 weeks of infection

Nidecker A "Adenovirus Tied to Low Cholesterol Obesity" Family Practice News May 15, 1997 page 9

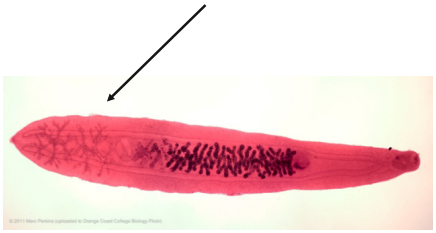
I Am Overweight Because I Caught A Virus

n=199	Antibody + for adenovirus 36
Obese Patients	23/154
Lean Patients	0/45

Nidecker, A *Family Practice News* May 15, 1997 page 9

Adenovirus 36 and Obesity Was This Just a Fluke?

No, THIS is a Fluke



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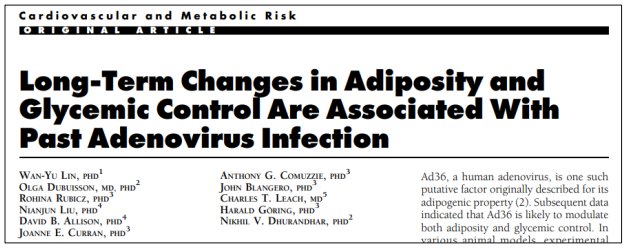


Cardiovascular and Metabolic Risk
ORIGINAL ARTICLE

Long-Term Changes in Adiposity and Glycemic Control Are Associated With Past Adenovirus Infection

WAN-YU LIN, PHD[1]
OLGA DUBUISSON, MD, PHD[2]
ROHINA RUBICZ, PHD[3]
NIANJUN LIU, PHD[3]
DAVID B. ALLISON, PHD[4]
JOANNE E. CURRAN, PHD[3]
ANTHONY G. COMUZZIE, PHD[3]
JOHN BLANGERO, PHD[3]
CHARLES T. LEACH, MD[5]
HARALD GÖRING, PHD[3]
NIKHIL V. DHURANDHAR, PHD[2]

Ad36, a human adenovirus, is one such putative factor originally described for its adipogenic property (2). Subsequent data indicated that Ad36 is likely to modulate both adiposity and glycemic control. In various animal models, experimental

N = 1,400

Lin WUY, et al *Diabetes Care* 2013;36:701-707

I'm Overweight Because
My Vitamin D is Too Low

FROM THE JOURNALS

Does vitamin D deficiency cause obesity or vice versa?

Publish date: December 29, 2022

By Caroline Apovian, MD

Family Practice News

Apovian C Fam Pract News 2022;December 29

I am Overweight Because of Insufficient Vitamin D

"A recent study found that people with obesity have lower blood levels of vitamin D….This association…has led to much speculation on whether low vitamin D levels cause obesity or whether obesity causes low vitamin D levels."

Apovian C Fam Pract News 2022;December 29

I am Overweight Because of Insufficient Vitamin D

" The interest in this topic is piqued by the possibility that if vitamin D deficiency causes obesity, perhaps Rx could be as simple as providing vitamin D supplementation….."

Apovian C Fam Pract News 2022;December 29

I'm Overweight Because
My Intestinal Bacteria Are Imbalanced

I Am Overweight Because of My Intestinal Bacteria

- Observation: Conventionally raised mice have 42% more total body fat than mice raised in germ-free environs
  - Despite 29% *more* calories ingested by germ-free mice
- Addition of GI flora to germ-free mice→ 60% body fat increase within 14 days

Henry J "Is Bacteria to Blame for Obesity" *DOCNEWS* 2007;April:p 6

I'm Overweight Because My Sympathetic Nervous System Is Sluggish

A Low Sympathoadrenal Activity is Associated with Body Weight Gain and Development of Central Adiposity in Pima Indian Men

P. Antonio Tataranni, James B. Young, Clifton Bogardus, Eric Ravussin*

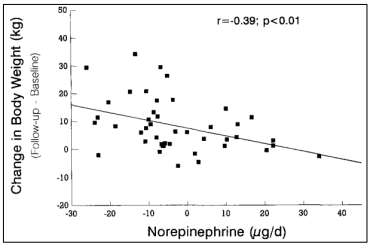
Obesity Research 1997;5(4):341-347

SNS and Weight Gain

- Non-diabetic Pima Indian men (n=44)
- Mean f/u = 3.3 years (0.5-7.4 yrs)
- Mean wt gain = 8.4 kg (5.9kg-34.4kg)
- Outcome: Correlation between norepinephrine and epinephrine daily secretion and weight gain

Tataranni PA, et al *Obesity Research* 1997;5(4):341-347

SNS Activity Inversely Related to Weight Gain



N = 44 non-diabetic Pima Indian Men

Tataranni PA, et al *Obesity Research* 1997;5(4):341-347

SNS Activity Inversely Related to Weight Gain

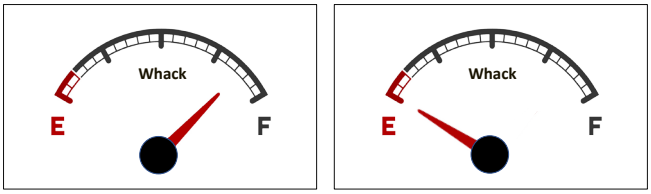
"....these findings suggest, for the first time in humans, that a low sympathoadrenal function is associated with body weight gain and development of central adiposity."

Tataranni PA, et al Obesity Research 1997;5(4):341-347

I'm Overweight Because

My Chromosome 15q11-q13 is Out of Whack

Whack Level Gauge



Whack 6/8 Full

Out of Whack

Genetic Obesity Syndromes: Prader-Willi

"…chromosomal deletions on…chromosome 15q11-q13 cause Prader–Willi syndrome, a complex neurodevelopmental disorder that includes hyperphagia as a cardinal Sx.

Wevrick R *Physiology & Behavior* 2020;219:1-7

Pharmacotherapy

Gastroenterology 2022;163:1198–1225

GUIDELINES

AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity

Eduardo Grunvald,[1,*] **Raj Shah**,[2,*] **Ruben Hernaez**,[3,4,5,*] Apoorva Krishna Chandar,[6] Octavia Pickett-Blakely,[7] Levi M. Teigen,[8] Tasma Harindhanavudhi,[9] Shahnaz Sultan,[10] Siddharth Singh,[11] and Perica Davitkov,[6,12] on behalf of the AGA Clinical Guidelines Committee

Why START With Pharmacotherapy
An Honest Appraisal of Lifestyle

"Lifestyle intervention is the foundation for management of obesity, but it has limited effectiveness and durability for most individuals."

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

AGA Pharmacologic Rx for Obesity
Opening Statement

"Pharmacological management of obesity improves outcomes and decreases the risk of obesity-related complications. This AGA guideline is intended to support practitioners in decisions about pharmacological interventions for overweight and obesity."

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

WHO Should Be Treated?
It's Always "In Addition to" not "Instead of" Lifestyle

"The panel strongly recommended the use of pharmacotherapy in addition to lifestyle intervention in adults with overweight and obesity (BMI ≥30, or ≥27 with weight-related complications) who have an inadequate response to lifestyle interventions."

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Potential Benefits of MEDs
Endocrine Society Clinical Practice Guideline

"Drugs may amplify adherence to behavior change and may improve physical functioning such that increased physical activity is easier in those who cannot exercise initially."

Apovian CM et al *JCEM* 2015;100(2):342-362

Weight Loss Meds: How Long to Rx?

"Historically, patients and providers thought that weight loss meds could be used to produce an initial weight loss that could subsequently be sustained by behavioral means. The available evidence does not support this view."

Apovian CM et al *JCEM* 2015;100(2):342-362

Pharmacotherapy: General Principles

- F/U: at least monthly X 3 then at least q 3 months ongoing
- Efficacy threshold: 5% at 3 months

"If deemed ineffective (weight loss <5% at 3 mo)…we recommend that the medication be discontinued...."

Apovian CM et al *JCEM* 2015;100(2):342-362

AGA Obesity Pharmacology Therapy* Guideline
9 Key Recommendations When Lifestyle Is Not Enough

1) Add pharmacological agents, which generally need to be used chronically
2) Add semaglutide 2.4 (1st line)
3) Add liraglutide 3.0 mg (2nd line)
4) Add phentermine-topiramate ER (2nd line)
5) Add naltrexone-bupropion ER (2nd line)

*For BMI ≥30 or ≥27 with weight related complications

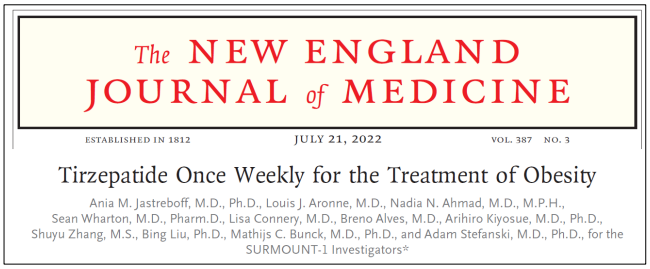
Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

AGA Obesity Pharmacology Therapy* Guideline
9 Key Recommendations When Lifestyle Is not Enough

6) Do not use orlistat
7) Add phentermine (3rd line)
8) Add diethylpropion (3rd line)
9) Only use Gelesis 100 in clinical trial setting

*For BMI ≥30 or ≥27 with weight related complications

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

Jastreboff AM, et al *NEJM* 2022;387(3):205-216

What is Tirzepatide?

- Peptide sequenced from native GIP (Glucose-dependent insulinotropic polypeptide)
- Amino acid substitutions
- GIP receptor agonist
- GLP1 receptor agonist (5 X weaker than native GLP)

Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Obesity: Tirzepatide in Non-DM

- Study: RDBPCT Overweight/Obese Adults (n =2,539)
- Inclusion:
  - BMI ≥30 (94.%)
  - BMI ≥27 + nonDM comorbidity*
- Rx: tirzepatide SQ 5mg,10 mg,15 mg weekly vs PBO
- Coprimary Endpoints (at 72 weeks):
  - % weight change from baseline
  - % with ≥5% weight loss

*HTN, CVD, OSA, Lipids

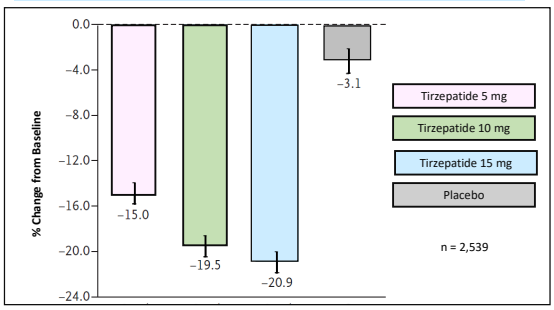
Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide in Non-DM: AEs

- "the most common AEs with tirzepatide were GI, and most were mild-moderate…occurring primarily during dose escalation."
- Discontinuation rates
  - 5 mg: 4.3%
  - 10 mg: 7.1%
  - 15 mg: 6.2%
  - Placebo: 2.6%

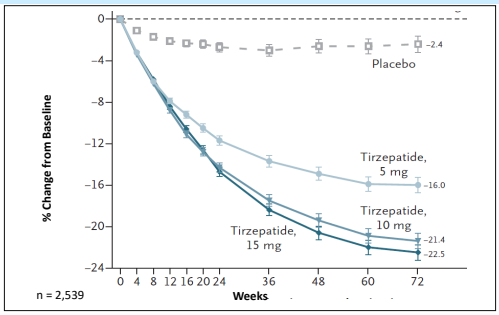
Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide: Overall % Δ Body Weight
Baseline - 72 weeks



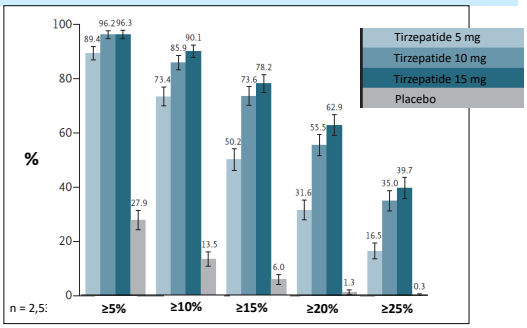
Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide: Overall % Δ Body Weight
Baseline - 72 weeks



Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide: % Achieving Weight Loss Thresholds



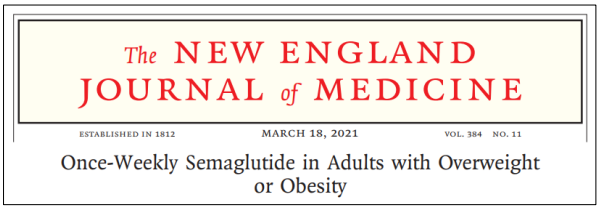
Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide: So, the Weight Comes Off
WHERE Does It Come off From?

CHANGE IN BODY COMPOSITION

"The mean reduction in total body fat mass was 33.9% for tirzepatide, as compared with 8.2% for with placebo…."

Jastreboff AM, et al *NEJM* 2022;387(3):205-216



Wilding JPH, et al *NEJM* 2021;384(11):989-1002

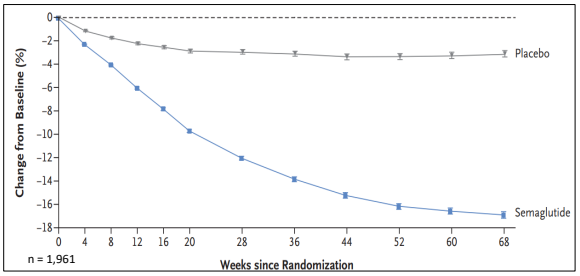
Semaglutide: Overweight/Obesity (nonDM)

- Study: DBRPCT adults (n=1,961)
- Inclusion
  - BMI ≥30
  - BMI ≥27 with nonDM comorbidities*
- Rx: Semaglutide 2.4mg SC weekly vs placebo
- Coprimary Endpoints (at 68 weeks)
  - % weight reduction
  - % ≥5 weight reduction

*HTN, CVD, OSA, Lipids

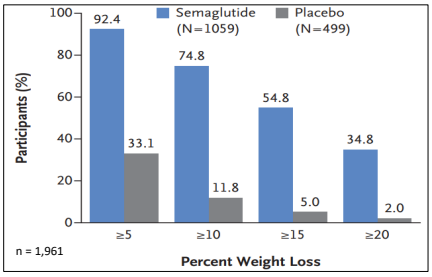
Wilding JPH, et al *NEJM* 2021;384(11):989-1002

Semaglutide 2.4mg SQ: %Wt Δ From Baseline
Per Protocol Analysis



Wilding JPH, et al *NEJM* 2021;384(11):989-1002

Semaglutide SQ: %Wt Δ From Baseline
Per Protocol Analysis (at 68 Weeks)



Wilding JPH, et al *NEJM* 2021;384(11):989-1002

Semaglutide
AGA Obesity Pharmacology Guideline: the 'Fine Print'

1) 1st line because of greatest degree of weight loss
2) Approved for DM
3) Titrate gradually to mitigate GI adverse effects
4) Note association with pancreatitis and gallbladder disease

*For BMI ≥30 or ≥27 with weight related complications

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Semaglutide Dosing Schedule: Wegovy vs Ozempic

	Ozempic (SQ Weekly)	Wegovy (SQ Weekly)
Initial	0.25 mg	0.25 mg
At 4 weeks	0.5 mg	0.50 mg
At 8 weeks	1.0 mg	1.0 mg
At 12 weeks	2.0 mg	1.7 mg
At 16 weeks	No dose increase	2.4 mg

Wegovy PI, accessed 1/2/23;Ozempic PI, accessed 1/2/23

Semaglutide & Weight Loss: Real World Data
Non-diabetics (Mostly)

JAMA Network | Open

Original Investigation | Nutrition, Obesity, and Exercise

Weight Loss Outcomes Associated With Semaglutide Treatment for Patients With Overweight or Obesity

Wissam Ghusn, MD; Alan De la Rosa, MD; Daniel Sacoto, MD; Lizeth Cifuentes, MD; Alejandro Campos, MD; Fauzi Feris, MD; Maria Daniela Hurtado, MD, PhD; Andres Acosta, MD, PhD

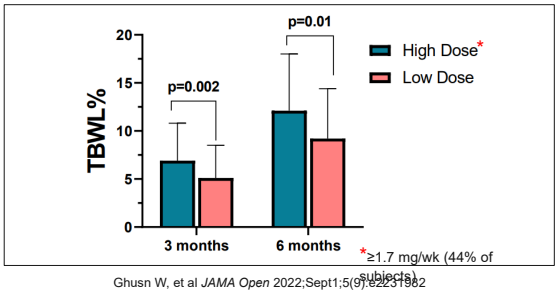
Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Semaglutide & Weight Loss: Real World Data
Non-diabetics (Mostly)

- Study: Retrospective Cohort Study (n=175)
- Inclusion (Mayo Clinic Rochester):
  - Adult (mean age = 49.3)
  - Overweight/Obese (mean BMI = 41.3)
  - Predominantly non-diabetic (84%)
- Rx: Semaglutide 2.4 mg SQ weekly X 6 months
- Outcome: % weight loss

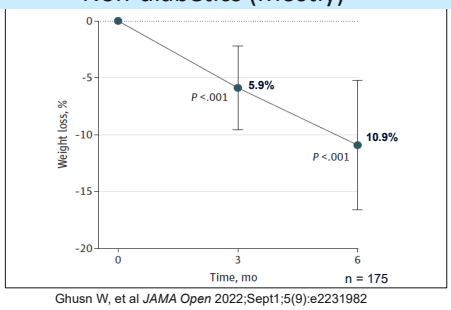
Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Semaglutide & Weight Loss: Real World Data
Non-diabetics (Mostly)



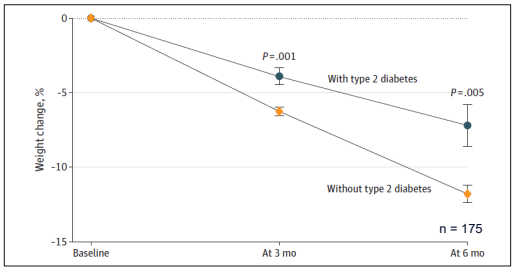
Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Semaglutide & Weight Loss: Real World Data
Non-diabetics (Mostly)



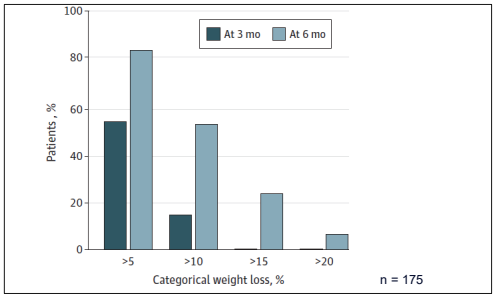
Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Semaglutide & Weight Loss: Real World Data
Non-diabetics (Mostly)



Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Semaglutide & Weight Loss: Real World Data
Non-diabetics (Mostly)



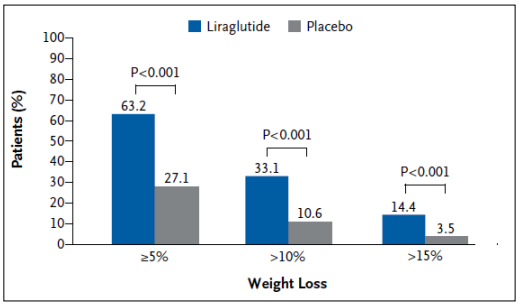
Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Liraglutide 3 mg/d (Saxenda): Wt Loss

- Study: RDBPCT adults (n=3,731)
- Rx: liraglutide 3 mg/d vs placebo x 56 wks
- Inclusion
  - BMI >30
  - BMI >27 + HTN or dyslipidemia
- Outcomes
  - Weight change
  - % losing ≥5%
  - % losing ≥10%

Pi-Sunyer X et al *NEJM* 2015;373(1):11-22

Liraglutide 3 mg/d: Wt Loss



Pi-Sunyer X et al *NEJM* 2015;373(1):11-22

JAMA | Original Investigation

Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes
The STEP 8 Randomized Clinical Trial

Domenica M. Rubino, MD; Frank L. Greenway, MD; Usman Khalid, MD, PhD; Patrick M. O'Neil, PhD; Julio Rosenstock, MD; Rasmus Sørrig, MD, PhD; Thomas A. Wadden, PhD; Alicja Wizert, PhD; W. Timothy Garvey, MD; for the STEP 8 Investigators

Rubino DM, et al *JAMA* 2022;327(2):138-150

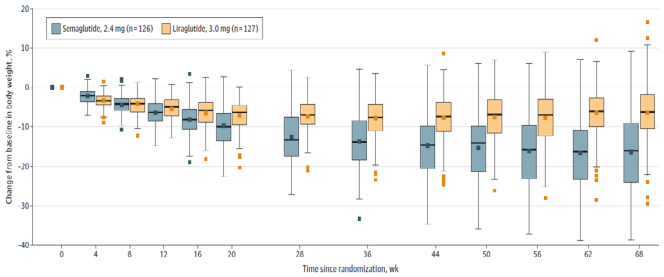
OBESITY: SQ Semaglutide vs Liraglutide

- Study: RPOLT Obese/overweight adults (n=338)
- Inclusion
  - BMI 30
  - BMI 27 + Comorbidities*
- Exclusion: DM
- Rx: semaglutide 2.4 mg qwk vs liraglutide 3.0 mg qd
- 1^0 Endpoint (at 68 weeks): % change body weight

*HTN, dslipidemia, OSA, CVD

Rubino DM, et al *JAMA* 2022;327(2):138-150

OBESITY: SQ Semaglutide vs Liraglutide



Rubino DM, et al *JAMA* 2022;327(2):138-150

Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial

Gadde, KM Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers MI, Day WW

Lancet 2011;377:1341-52

CONQUER

is a clever Acronym for

CONQUER

CONQUER
Overweight + Comorbidities

- Study: RDBPCT overweight/obese subjects (BMI 27-45 kg/m^2) + comorbidities (n=2,487)
- Comorbidities (≥2)
  - HTN
  - Prediabetes/DM
  - Dyslipidaemia
  - Abdominal obesity
- Rx (X 56 weeks):
  - Phentermine/topiramate CR 7.5/46 mg QD
  - Phentermine/topiramate CR 15/92 mg QD
  - Placebo

Gadde KM, et al *Lancet* 2011;377:1341-52

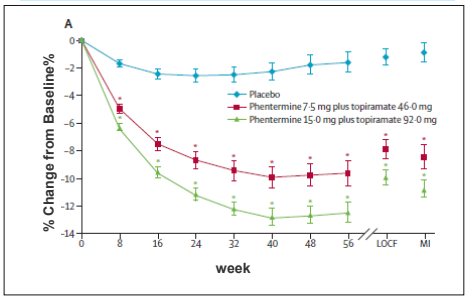
CONQUER
Overweight + Comorbidities

PRIMARY ENDPOINTS
- % change in body weight
- Proportion of patients achieving ≥5% wt loss

SECONDARY ENDPOINTS
- Weight loss
- Proportion of patients achieving >10% wt loss
- Change in waist circumference

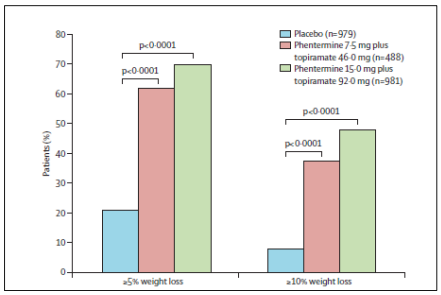
Gadde KM, et al *Lancet* 2011;377:1341-52

CONQUER: Weight Loss Thru 56 Weeks



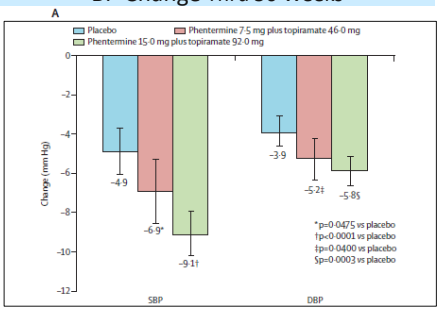
Gadde KM, et al *Lancet* 2011;377:1341-52

CONQUER: Weight Loss Thru 56 Weeks



Gadde KM, et al *Lancet* 2011;377:1341-52

CONQUER: BP Change Thru 56 Weeks



Gadde KM, et al *Lancet* 2011;377:1341-52

Two-year Sustained Weight Loss & Metabolic Benefits with Controlled-Release Phentermine/Topiramate in Obese and Overweight Adults (SEQUEL): a Randomized, Placebo-controlled, Phase 3 Extension Study

Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, Schwiers M, Day WW, Bowden CH

Am J Clin Nutr 2012;95:297-308

SEQUEL

is a clever acronym for

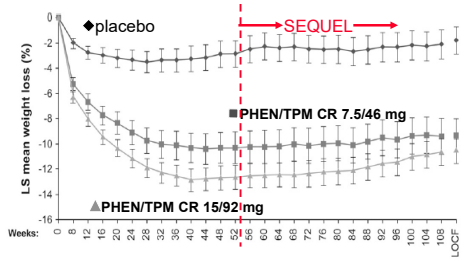
SEQUEL

SEQUEL

- Study: RPCT 52 wk extension of CONQUER
- Method: Subjects (n=676) continuing randomly assigned phentermine/topiramate or placebo from year 1
- Endpoint: Sustained weight loss

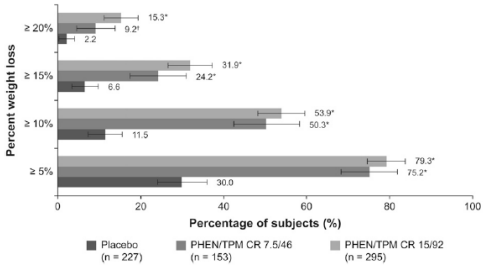
Garvey WT et al *Am J Clin Nutr* 2012;95:297-308

SEQUEL: Results Baseline to Week108



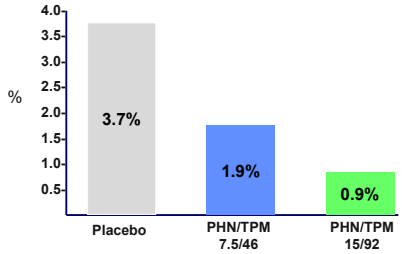
Garvey WT et al *Am J Clin Nutr* 2012;95:297-308

SEQUEL Results: Baseline to Week 108



Garvey WT et al Am J Clin Nutr 2012;95:297-308

SEQUEL: Progression to DM2



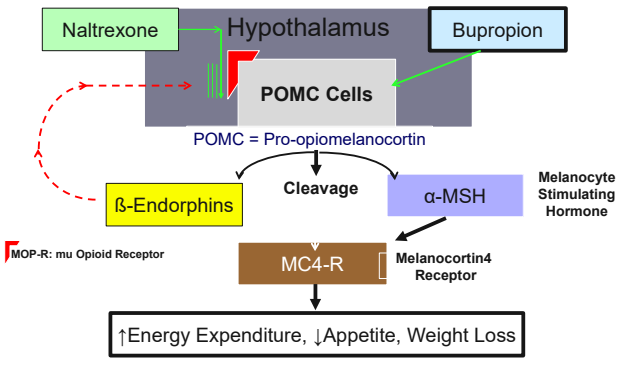
Garvey WT et al *Am J Clin Nutr* 2012;95:297-308

Phentermine/Topiramate CR (Qysmia) Prescribing Information

DOSAGE and ADMINISTRATION

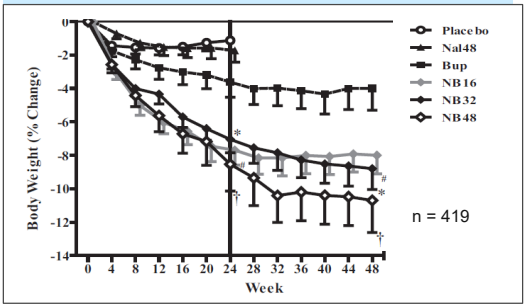
- Take QD in morning. Avoid evening dose to prevent insomnia
- Recommended dose: Qsymia 3.75/23 mg CR daily X 14 days, then increase to 7.5 mg/46 mg daily
- Discontinue or escalate dose if 3% weight loss is not achieved after 12 weeks on 7.5mg/46 mg dose
- Discontinue Qsymia if 5% weight loss is not achieved after 12 weeks on maximum daily dose of 15 mg/92 mg
- Discontinue 15 mg/92 mg dose gradually to prevent possible seizure
- Do not exceed 7.5 mg/46 mg dose for patients with moderate-severe renal impairment or patients with moderate hepatic impairment

Bupropion/Naltrexone Trials (Contrave)



Adapted from Billes SK et al *J Pharmacological Research* 2014;84:1-11

Naltrexone/Bupropion: Proof of Concept



Greenway FL et al *J Clin Endocrinol Metab* 2009;94(12):4898-4906

Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

*Frank L Greenway, Ken Fujioka, Raymond A Plodkowski, Sunder Mudaliar, Maria Guttadauria, Janelle Erickson, Dennis D Kim, Eduardo Dunayevich, for the COR-I Study Group**

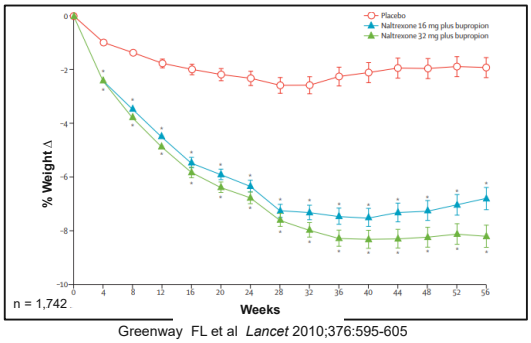
Greenway FL, et al. *Lancet* 2010; 376: 595–605

The Contrave Obesity Research Study-1 (COR-1)

- Study: RDBPCT Obese adults (n=1742)
- Rx (all given as 2 tabs b.i.d. x 56 weeks):
  - Naltrexone 4mg/bupropion SR 90 mg
  - Naltrexone 8mg/bupropion SR 90 mg
  - Placebo
- Outcomes (coprimary)
  - % weight loss
  - % achieving ≥ 5% wt loss

Greenway FL et al *Lancet* 2010;376:595-605

The Contrave Obesity Research Study-1 (COR-1)



Greenway FL et al *Lancet* 2010;376:595-605

Contrave Dosing

----------DOSAGE AND ADMINISTRATION----------

CONTRAVE dose escalation schedule (2.1):

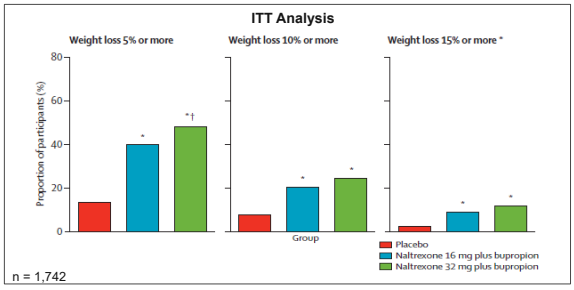
	Morning Dose	Evening Dose
Week 1	1 tablet	None
Week 2	1 tablet	1 tablet
Week 3	2 tablets	1 tablet
Week 4 – Onward	2 tablets	2 tablets

----------DOSAGE FORMS AND STRENGTHS----------

Extended-Release Tablets: 8 mg naltrexone HCl /90 mg bupropion HCl

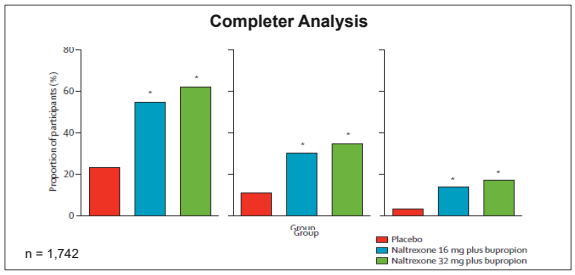
Contrave Prescribing Information

The Contrave Obesity Research Study-1 (COR-1)



Greenway FL et al *Lancet* 2010;376:595-605

The Contrave Obesity Research Study-1 (COR-1)



Greenway FL et al *Lancet* 2010;376:595-605

The NE-Releasing Agents

	Phentermine	Diethylpropion
Trade Names	Adipex, Ionamin	Tenuate
Dose	37.5 mg/d (Adipex) 30-37.5 mg/d (Ionamin)	75 mg/d
MOA	NE-Release	
Indications	Short-term (3 months)	
Weight loss* (Study duration)	3.6 kg (2-24 wks.)	3 kg (6-52 wks.)
Example AEs	HA, HTN, tachycardia, insomnia, dry mouth, constipation, PVCs, ED	
Contraindications	Anxiety, CHD Hx, HTN (uncontrolled), MAO-I, PG, breast feeding, glaucoma, hyperthyroid	
	*weight loss *above* lifestyle alone	

Apovian CM, et al *J Clin Endocrinol Metab* 2015;11(2):342-362

Endocrine Society Position
Long-Term Phentermine: Yes *IF*

"Given the wide clinical prescribing of phentermine for >20 years and the lack of evidence of serious side effects, even in the absence of long-term controlled safety and efficacy data it seems reasonable for clinicians to prescribe phentermine long term as long as…."

Apovian CM, et al *J Clin Endocrinol Metab* 2015;11(2):342-362

Phentermine or Diethylpropion
AGA Obesity Pharmacology Guideline: the 'Fine Print'

1) Only approved for 12 weeks, but may use longer off-label
2) Avoid if Hx CVD
3) Monitor BP and heart rate periodically

*For BMI ≥30 or ≥27 with weight related complications

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Meds NOT RECOMMENDED for Long Term Management

Agent	Comment
Orlistat (Xenical, Alli)	Suggest AGAINST
Superabsorbent Hydrogel (Gelesis 100, Plenity)	Knowledge Gap

Adapted from Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Orlistat
AGA Obesity Pharmacology Guideline: the 'Fine Print'

1) May consider in patients potentially satisfied with small amount of weight loss and tolerant of GI adverse effects
2) Provide vit A,D,E,K multivitamin supplement (2-hour gap)

*For BMI ≥30 or ≥27 with weight related complications

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Cautions in Use of Anti-obesity Medications
AGA Obesity Pharmacology Therapy Guideline

- Pregnancy: NOT
- T2DM: Consider potential for hypoglycemia
- HTN: Consider potential for hypotension
- Bulemia nervosa: NOT
- Binge Eating Disorders: monitor for decompensation

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Conclusions

- We are beginning to understand the complexity of obesity
- Highly effective pharmacologic agents are available
- Expert guidelines recognize the stark limitations of lifestyle alone in achieving health goals, and now condone early and sustained pharmacotherapy, suggesting obesity be included in the chronic disease model

SELF EVALUATION

Obesity: Primary Care Management

1. A BMI >30 is the current threshold for the diagnosis of obesity. Which items below might falsely elevate BMI?
    a. Ascites
    b. Edema
    c. Heart Failure
    d. Treatment with a thiazolidinedione
    e. All of the above

2. A 52 y.o. otherwise healthy woman has a BMI of 32 after her best efforts at incorporating diet and exercise. If she starts pharmacotherapy for weight management, what regimen might be anticipated?
    a. Limit pharmacotherapy to 3 months
    b. Limit pharmacotherapy to 6 months
    c. Limit pharmacotherapy to 1 year
    d. Consider long-term (i.e., indefinite) Rx

3. The cause of obesity is?
    a. Habitual ingestion of markedly excess calories
    b. Most commonly hypothyroidism
    c. Difficult to definitively discern in any one individual, but numerous potential pathologic etiologies other than simple overeating are possible
    d. Most commonly steroid excess (e.g, Cushing's disease)

4. Which pharmacotherapeutic agent below has shown the greatest degree of weight loss (not necessarily from head-to-head trials)?
    a. Semaglutide
    b. Liraglutide
    c. Dulaglutide
    d. Tirzepatide

5. How does naloxone help bupropion to induce weight loss?
    a. Naloxone causes weight loss independently, so the results are additive
    b. Naloxone causes calorie malabsorption
    c. Naloxone blocks the feedback loop that shuts off pro-opiomelanocortin production
    d. Naloxone increases thyroid hormone efficacy

Answer Key: 1. E, 2. D, 3. C, 4. D, 5. C

Elizabeth M. Prusak, MD, FACOG

Elizabeth M. Prusak, MD, FACOG, of Indianapolis, Indiana is board certified by the American Board of Obstetricians and Gynecologists as well as the North American Menopause Society. In addition to private practice, she is an American Board of Gynecology oral board exam instructor as well as an educator, private instructor and medical writer. Dr. Prusak utilizes a holistic approach in her practice and has spoken nationally to medical audiences on managing patients with difficult gynecological issues.

You may contact Dr. Prusak with your questions and comments by email at ElizabethPrusak@Yahoo.com.

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Gynecology Screening

Screening

- To detect disease among healthy population
- Without symptoms of disease
- To decrease mortality due to the disease screened

Disease Appropriate Screening

- High prevalence of disease
- Known natural history, precursor lesion, and course of progression
- Detection of early stage disease, amenable to cure
- Method used is simple, cheap, specific and sensitive, acceptable, risk free

Gynecologic Screenings

- Cervical Cancer
- Ovarian Cancer
- Endometrial Cancer
- Breast Cancer
- Vulvar/Vaginal Cancer

Carcinoma of the Cervix

- Most common genital tract cancer
- Median age: 50

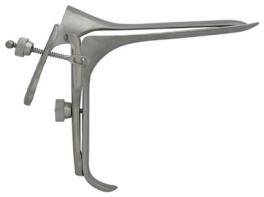
Natural History of Low Grade HPV Cervical Lesion

- Cervical HPV is very common, related to sexual activity
- High spontaneous remission rate
- LSIL progresses to HSIL in 10 years
- HPV testing combined with pap smear improves screening

When Not to Take a Cervical Smear

- Blood in vagina
- Obvious lesion which would need biopsy
- Cervix cannot be seen

Pederson Vaginal Speculum



How to Manage an Abnormal Pap?

- Pap results will result according to Bethesda classification system
- Management will be according to ASCCP guidelines
- Referral to a Gynecologist is always appropriate because guidelines can be confusing

Management of Abnormal Pap

- Watchful waiting and repeat
- Colposcopy with/without biopsy
- LEEP/CONE procedure in office
- Hysterectomy

Ovarian Cancer

- 4th most common cause of cancer mortality
- Most ovarian cancers are diagnosed at advanced stages
- Family history especially BRCA mutations are important in risk stratification and screening

Types of Ovarian Cancers

- Epithelial (most common)
- Germ Cell
- Sex Cord
- Metastatic

Ovarian Cancer Symptoms

- Most are asymptomatic
- Lower abdominal pain and pressure
- Mass in the abdomen
- Vaginal Bleeding
- Bowel symptoms

Why is Screening for Ovarian Cancer Difficult?

- Lack of well defined precursor lesion
- Lack of a good method
- Anatomic location of the ovary is not easily accessible

Ovarian Cancer Screening Tests

- Recommended only for high risk patients, such as Lynch Syndrome and BRCA carriers
- Serum CA125 and ultrasound
- Not cost effective or accurate
- Not in general population

Endometrial Cancer

- Majority are detected by symptoms: Postmenopausal Bleeding
- High Cure rate for early stage disease
- Endometrium is “easy” to sample

Endometrial Cancer Screening

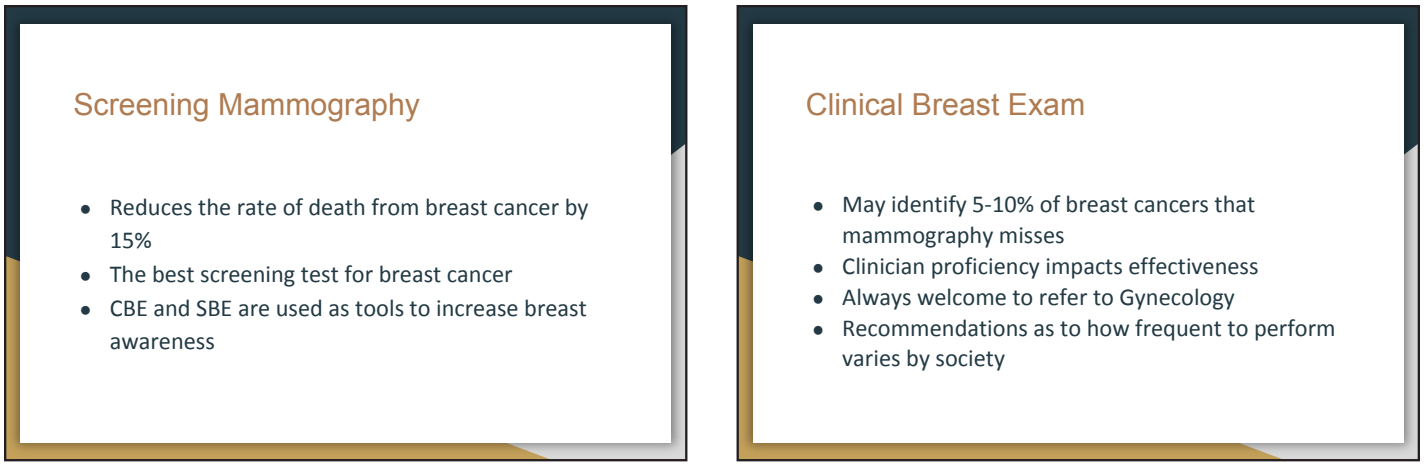
- Not indicated for general population
- Important in syndrome called Lynch Syndrome
- Pelvic ultrasound and endometrial biopsy

Vaginal/Vulvar Cancer

- Rarer types of Gynecologic Cancers
- Usually asymptomatic until it becomes larger
- No approved screening test
- Recommend yearly pelvic examination

Breast Cancer

- Screening tests include mammography, clinical breast exam and self breast exams



SELF EVALUATION

Gynecology Screening

True/False

1.___ The most common genital tract cancer is cervical cancer

2.___ LSIL pap progresses to HSIL in 1-2 years.

3.___ Most ovarian cancers are detected and diagnosed at an early curable stage.

4.___ The best screening test to detect breast cancer is the clinical breast exam.

5.___ The clinical breast exam identifies 10-15% of cancers that mammogram might not detect.

6.___ The most common symptoms of endometrial cancer is postmenopausal bleeding.

7.___ Endometrial cancer screening is not recommended for the general population.

Answer Key: 1. T, 2. F, 3. F, 4. F, 5. T, 6. T, 7. T

Thomas P. Cox, ARM

Thomas P. Cox, ARM, of Richmond, Virginia, is president of Bluewater Solutions, LLC, a boutique risk and insurance management company focusing primarily on health care and related risks. He has over 30 years of experience working almost exclusively with health care professionals. Mr. Cox has held executive positions with a large medical center, a major medical malpractice insurance company, and multiple insurance agencies before starting Bluewater Solutions in 2009. Bluewater Solutions offers all manner of risk and insurance management, consulting, and litigation stress coaching. Mr. Cox has a B.S. in Health Education, has done graduate work in Public Health, and earned his Associate in Risk Management designation from the Insurance Institute of America.

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Understanding Insurance Gaps and Managing Litigation Stress

Insurance Gaps

- Personal v. Professional
  - Cyber Liability
  - Disability insurance
  - Life Insurance
  - Supplemental benefits

Personal v. Professional

- The last section will deal with litigation stress, where I will discuss that who you are is what you do and what you do is who you are.
- Example: Insurance company v. dental or medical practice

Personal v. Professional

- If it is difficult separating who you are from what you do, then any insurance gap is both personal and professional.
- When dealing with litigation, who you are makes it more difficult to deal with than other professions.

Cyber Liability

Basics

- First internet breach: 1974
- Victims: American Express, Visa, MasterCard
- 300,000 job openings in cyber security
- Good guys always one step behind bad guys

Cyber Liability Basics

- Remove the internet = estimated 8% decrease in GDP
- Threat: More ways to get money out of the internet and more easily (do not need to buy a gun)
- Continual changes in software leaves holes
- The cloud (where the data is going, so is the action)
- The Internet of Things ("IoT") (*Phones, watches, house*)
- "It can't happen to me..."
- Professional and personal…one and the same
- Will likely be how WWIII starts

Cyber Liability Basics

- What is cyber crime?

Unlawful acts wherein the computer is either a **tool** or **target** or both. Commonly it is a crime that can be committed live (analog) or via computer (digital).

  - Illegal sales (stolen goods, illegal drugs)
  - Pornography
  - Online gambling
  - Intellectual property theft
  - Defamation
  - Stalking

Cyber Liability Basics

Basics

- Over 300 billion emails sent daily
- Approximately 50% are phishing
- Looking for data to sell or leverage
- Personal or customer information

Cyber Liability Basics

- 95% of phishing-based breaches follow software installation.
- $3.62 million: average cost of an email breach.
- 66 days: Average time needed to remediate a breach.
- 27.7%: Likelihood a second breach will occur with 24 months.
- $141: average cost per record to remediate a breach, but some industries are hit harder than others:
  - > Healthcare: $380 per record
  - > Financial services: $245
  - > Human Services: $223
  - > Education: $200
  - > Life science: $188

Cyber Liability

- Having an incident response team can reduce the cost of a breach by approximately $19 per record

Cyber Liability Basics

- What is cyber crime?

The computer may, however, also be a *target* for unlawful acts.

- Unlawful access to a computer/system/network
- Theft of information
- E-mail bombing
- Trojan attacks
- Internet time theft
- Physical damage to a computer/system/network
- Ransomware

Cyber Liability Basics

Malware and non-malware attacks

- Malware attacks involve emails with infected attachments used to gain access to a computer, commonly pdf or doc.
- Attacks without malware impersonate a trusted person or company to trick the user into giving away corporate information or assets. These commonly use imitation login pages, malicious links, or forged requests.
- 91% of cyber crime starts with **one** email -*FireEye*

Cyber Liability Basics

- 10% of attacks involve malware
  - Viruses
  - Worms
  - Ransomware
  - Adware
  - Trojan Horse
  - Spyware

Cyber Liability Basics

- 90% of email attacks do not involve malware
  - Impersonation
  - CEO fraud
  - Whaling
  - Spear phishing
  - Credential harvesting
  - W2 scams

Cyber Liability Basics

Two biggest concerns, financially, are ransomware and theft of Personally Identifiable Information ("PII").

Ransomware attacks

- 97% infected attempted to infect backup repositories
- 53% of data was encrypted
- 34% of companies that paid the ransom were unable to recover data

Cyber Liability

Now that I have your attention…

- Cyber liability insurance comes with risk management, some offer monitoring
- Underwriting tracks size and revenue
- Premiums jumped in 2021 and 2022
- Premiums flattening in 2022 and 2023
- Make sure you know what you are buying

Cyber Liability

Insuring Clause 1. Cyber Incident Response

- Cyber incident response
- Legal and regulatory response
- Security and forensic costs
- Crisis communication costs
- Privacy breach management costs
- Third-party privacy breach management costs
- Post-breach remediation costs

Cyber Liability

Insuring Clause 2. Cyber Crime

- Funds transfer costs
- Theft of funds held in escrow
- Theft of personal funds
- Extortion
- Corporate identify theft
- Telephone hacking
- Customer phishing

Cyber Liability

Insuring Clause 3. System Damage and Business Interruption

- System damage and rectification costs
- System business interruption
- Claim preparation costs

Cyber Liability

Insuring Clause 4. Network Security & Privacy Liability

- Network security liability
- Privacy liability
- Contingent bodily injury
- Management liability
- PCI fines, penalties and assessments

Cyber Liability

Insuring Clause 5. Regulatory Actions

- Regulatory fines, penalties, and resolution agreements
- Corrective action plan costs

Insuring Clause 6. Media Liability

- Defamation
- Intellectual property rights infringement

Insuring Clause 7. Technology errors and omissions

Insuring Claus 8. Court attendance costs

Cyber Liability

- The key point is to have this coverage while also working with a reputable service provider. Between these two resources you should have the best protection possible and also be protected in the event of a successful cyber attack.

Insurance Gaps: Disability insurance

- What it does
- Why does it matter?
- What are the options?

Disability insurance

What it does

- Income protection

Why do you need it?

- >25% likelihood of disability between 20-65
- People dismiss spinal cord and brain injuries, and amputation as too remote, but most disability claims are related to cancer, back injury, heart attack, diabetes, and other chronic illnesses (see “exposome” in Part 1).

Disability insurance

Types of disability insurance

Short-term

Long-term

Individual

Group

Short-term disability

- Typically replaces 60-70% of base salary
- Term is a few months to one year
- Likely will have an elimination period of as few as a couple of weeks to a month
- May or may not cover partially disabled

Long-term disability

- Typically replaces 40%-65% of base salary
- Common elimination period is 90 days
- Benefits end when:
  - Disability ends
  - At a certain age or number of years
  - Social Security Normal Retirement ("SSNR")

Definition of disabled

- Any occupation – least expensive
- Modified own occupation
- Transitional own occupation
- Own occupation
- Own occupation not engaged
- Own specialty – most expensive

Policy, not marketing materials or agent

Disability Policy Riders

- Partial/Residual Disability
- Inflation
- Future Purchase
  - Future increase
  - Benefit update
  - Benefit purchase
  - Benefit increase
- Catastrophic Disability
- Retirement
- COLA
- Additional Disability
- Non-Cancelable and Guaranteed Renewable

Disability Policy Riders

- Must have
  - Guaranteed Renewable
    - Conditionally renewable = NO
    - Guaranteed renewable = premium?
    - **Non-Cancelable and Guaranteed Renewable**
  - Residual Disability
  - Own Specialty
  - COLA (under 50)
  - Future Purchase (under 30)

Group Disability

- Can cover people otherwise uninsurable
- Offers optional communicable disease coverage (Business Overhead)
- Will be a lower premium than individual
- Two or more professionals = group
- Can include group life insurance
- Employee benefit

Insurance Gaps: Life Insurance

Life Insurance Marketing and Research Association (LIMRA)

- Misconceptions are deterring millennials (ages 27-42) from buying the life insurance protection they need.
- According to the LIMRA 2022 Insurance Barometer Study:
  - 55% of millennials have no life insurance at all
  - 35% of millennials feel that life insurance is too expensive
  - 1/3 of millennials say they haven't purchased life insurance because they don't think they would qualify, or they haven't been approached

Life Insurance

- Asset protection
- Who you love and who you owe
- Individual and Group (term)
- Term Life: 100% death benefit with policy term
- Permanent Life
  - Whole Life: death benefit with savings component (cash value)
  - Universal Life: Whole life with the option to increase or decrease premiums (increase and decrease benefits)
  - Variable Life: Investment vehicle with premiums invested, typically in mutual funds

Final Expense Insurance

- Whole life insurance with a small benefit
  - Funeral or burial insurance
- Face value of $2,000 - $35,000
- Covers final expenses: Funeral, burial, cremation, taxes, debts ($7,000-$12,000)
- Likely don't need if you already have life insurance or pre-paid funeral expenses
- This does make sense for anyone younger than 85 with no life insurance or pre-paid funeral coverage
- Guaranteed issue, but maybe not on day 1

Supplemental Benefits

Indemnity-Based Voluntary Insurance

- Commonly specific coverage for cancer, hospital indemnity, accident, critical illness, etc.
- Offered by employers to employees, paid by employees
- No tax benefits
- No coverage outside of the scope

Supplemental Benefits

Expense Reimbursed Insurance

- Unique benefit plan that:
  - Allows for "discrimination"
  - Is ACA compliant
  - Is a fully-insured insurance plan and tax-deductible for employer
  - Fills coverage gaps (reimbursed insurance)
  - Is flexible
  - Enhances employee recruiting and retention
  - Helps with high-deductible health plans

Supplemental Benefits

- **Level 1: Benefit Gaps**

Deductibles, co-insurance, co-pays, exclusions, limitations, visit limits

- **Level 2: Expanded Coverage**

Brand name frames, private hospital room, major dental, additional PT visits, brand name prescriptions, OON mental health

- **Level 3: Unexpected coverage**

Acupuncture, adult orthodontia, LASIK, executive physicals, prescription sunglasses, prescribed massage therapy, treatment abroad

Expense Reimbursed Insurance

Expense reimbursed insurance isn't tied to the same types of condition limitations as indemnity-based voluntary insurance. This type of supplemental plan provides coverage for both routine expenses and beyond, casting a broader net of where coverage will be offered and leaving far fewer holes. If a coverage gap results from a routine Rx, a heart attack, cancer or anything in between, expense reimbursed insurance has the ability to provide coverage up to the specified plan levels, between $5,000 and $100,000.

Litigation Stress

Reader's Digest Version

- What is stress?
- Why does it occur?
- What should we do about it?
- What is litigation stress?
- Why does it occur?
- What should we do about it?
- Why should we do something about it?

Litigation Stress

How I ended up here

Stress

Some definitions

- General Adaptation Syndrome ("GAS")
- Stress
- Stressor
- Eustress
- Distress

Hans Selye

Stress

Selye's last inspiration for GAS came from an endocrinological experiment in which he injected mice with extracts of various organs. At first he thought he had discovered a new hormone, but then realized that anything he injected produced the same symptoms: swelling of the adrenal cortex; atrophy of the thymus; and, gastric and duodenal ulcers.

Stress

Paired with his observation that people with different diseases exhibit similar symptoms resulted in Selye describing the effects of "noxious agents," which he later termed "stress."

In other words, everything bothers us!

Stress

Selye eventually developed a theory of a physiology of stress having two components:

- A set of responses he eventually summarized as General Adaptation Syndrome; and,
- The development of a pathological state brought about from ongoing, unrelieved stress.

Stress

Selye discovered and documented that stress differs from other physical responses in that stress can originate from good news or bad, and whether the impulse is positive or negative. This eventually evolved into an understanding that there is the event, there is the response, and then there is our management of the response.

Example: Me

Stress

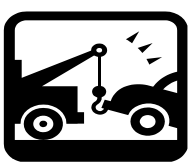
- Stress is something that happens to us on an ongoing basis, it is our reaction to the world around us.
- We perceive it as eustress or distress.
- The hypothalamic-pituitary-adrenal axis, the mechanism by which the body copes with stress, was also first described by Selye.
- Today it is usually summarized as the "fight or flight syndrome."

Stress

- The "fight or flight syndrome" is just as it sounds: the body is preparing to do something necessary for survival, preparing to fight or to run away.
- Very useful in the past and on occasion today.
- Much less useful today.
- Make everything life and death, you "die" a lot.

Stress

What happens if we are faced with stress that we cannot or should not fight or run away from? Think of an automobile where someone is stepping on the brake pedal and gas pedal at the same time. If you know nothing about how an automobile works you can still figure out that something bad is going to happen to that car…and to our bodies if we treat them the same way.



Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **Personality**
- **Training**
- **Injury**
- **System**

Litigation Stress

Most of the pioneering work on the subject of litigation stress was done by Sara C. Charles, M.D.

- Began her career at the University of Notre Dame College Mental Health Center
- 1972: Professor of Psychiatry and a practicing psychiatrist at the University of Illinois – Chicago
- 1976: Six-week malpractice trial; defense verdict
- Began litigation stress research
- 2005: Sara C. Charles, MD, Physician Litigation Stress Resource Center

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **Personality**

  The type of individual who enters the medical or dental profession is not only highly intelligent and driven but tends towards self-criticism. In addition, these individuals tend to be highly **independent**. In times of distress this independence can lead to isolation.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **Training**

  The survival mentality critical to successfully navigating medical and dental school, residency and, in some cases, fellowship, reward the independent, the driven, the self-critical. Doctors are trained to question constantly, even when a diagnosis and treatment are going well. When something goes wrong…

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **Training**

  The training a doctor receives leads to a practice that is normally stressful, but usually in equilibrium. However, with changes that have been going on in the U.S. health care system since 1980 doctors are feeling less in control over clinical decision-making than in the past.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **Injury**

  When diagnosis and treatment are going well, doctors are still questioning. When something goes wrong, the perfectionism and self-criticism of the doctor increases the normal stress, especially as someone has been injured. This does not happen with other professionals.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **Injury**

  In other words, if a doctor is sued for malpractice it is like an exclamation point at the end of a sentence or the proverbial straw that breaks the camel's back. The doctor has likely beaten him or herself up over what happened long before the claim or lawsuit shows up.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **System**

  In the tort system we currently have the most common way for an injured individual to be made whole, or as whole as possible, is through litigation. In litigation one person has to be right and one person has to be wrong.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **System**

  In a malpractice claim the patient is claiming the health care professional practiced bad medicine or dentistry, usually based on a **bad outcome**. Yet that outcome may have been the best possible outcome the patient could have expected.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **System**

  Add all of this up:
- A self-critical individual, the doctor,
- Who has had a bad outcome,
- Who is likely already questioning everything that was done, from the initial visit to the last patient encounter

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **System**

  And who now has an attorney (and eventually a plaintiff's expert and maybe the defense expert or insurance company) telling him/her that bad medicine was practiced, that it hurt someone, and that the doctor must pay.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **System**

  And in very simple terms, the litigation process is nasty. Doctors got to where they are today because they are scientists and they would like a malpractice claim to be a scientific inquiry. It is not. It is usually a circus, a theatre, unless Alternative Dispute Resolution is used, but…

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **System**

  Even if Alternative Dispute Resolution is used there will still be discovery before any mediation or arbitration, including a deposition, and the **deposition** is usually the nastiest part of the claim a doctor will have to deal with.

Litigation Stress

Professionals get sued all the time; why do health-care professionals seem to have such an extreme reaction?

- **System**

  In most states the claim process will follow a similar path:
- Service or Notice of Suit
- Discovery (Interrogatories and depositions)
- Settlement offers
- Alternative Dispute Resolution or Trial

Litigation Stress

What is the usual response to a claim of medical or dental malpractice?

- 95% of doctors have periods of extreme emotional distress during all or some portions of the litigation process.
- The distress may start with the bad outcome or it may start with the service of legal papers.
- The response will include, at various times, outrage, shock, dread, fear of reputation destruction, and fear over the financial impact.

Litigation Stress

What is the usual response to a claim of medical or dental malpractice?

- Feelings of intense anger, frustration, inner tension, and insomnia are frequent during the litigation process.
- 27%-39% of doctors report major depressive disorders
- 20%-53% report adjustment disorder
- 2%-15% report the onset or exacerbation of a physical illness.
- Less than 2% report drug or alcohol misuse

Litigation Stress

Why this extreme response?

- Go back to the characteristics of a doctor, the self-critical nature that leads to doubt when things are going well, the exaggerated sense of responsibility.
- In litigation fault must be established for compensation to be paid.
- Fault in a malpractice case is based on deviation from the standard of care, resulting in injury.
- Doctors bristle at the accusation that their care was “sub-standard.” It is an insult to their reputation, their honor.

Litigation Stress

Why this extreme response?

- A doctor looks at a claim of malpractice as a personal attack, whereas other professionals are able to look at it as a difference of opinion or the cost of doing business.
- Most people cherish their personal integrity and it is just that integrity that is under attack in a medical or dental malpractice claim, with the added challenge of a physical injury usually having occurred.

Litigation Stress

Other factors that come into play make each case unique:

- The doctor-patient relationship
- The nature and extent of the injury
- The publicity (or fear of it)
- The adversarial nature of litigation, which is foreign to how most doctors’ work.

The above contribute to feelings of isolation, frustration, dependency, and in general disrupt the usual equilibrium of the physician.

Coping with Litigation Stress

It has been determined through multiple studies over the years that the greatest sources of distress results from a lack of control or feelings of **lack of control**. Therefore, for physicians to cope with litigation, to regain the equilibrium necessary to reduce the distress, steps need to be taken to gain as much **control** as possible over a situation where control must be ceded to others.

Coping with Litigation Stress

Each of the following items is designed to help the doctor either gain control, gain a feeling of control, or not let the lack of control consume him/her (treat the symptoms).

Coping with Litigation Stress

1. Gain as much knowledge about the litigation process as possible. Do this through the attorney assigned to your case by your insurance company, or through the claims manager managing the claim for your insurance company, in order to maintain privilege.

Coping with Litigation Stress

2. Treat the symptoms. This is true for anyone dealing with stress, litigation or otherwise. When having a physical reaction, exercise eats up the juices of stress and work better over the long-term than medication, but medication may be necessary.

The Body Keeps the Score

Coping with Litigation Stress

3. Get a personal physician, if you do not have one. Get treatment for any persistent symptoms, such as a physical illness, depression, substance abuse, or the like. Do NOT self-diagnose or self-prescribe.

Coping with Litigation Stress

4. Make family important and a part of the process, and get help if needed to maintain strong family ties. A physician's wife once stated that she "lost" her husband for two years when he was sued for malpractice, that he was distant, unavailable, and "locked up inside of himself."

Unable to be present

Mindfulness

Coping with Litigation Stress

5. The quicker steps are taken, the less chance there is for better coping. If coping mechanisms are not put in place rapidly it can lead to additional malpractice claims (statistics have shown that claims do happen in clusters), along with loss of family and friends. In addition, if the equilibrium is too disrupted the doctor may become a hazard to the practice and to patients.

Coping with Litigation Stress

6. Social support can come from many sources. Most medical malpractice insurance companies have physician support programs today. These exist for two primary reasons, better defense and reduced chance of additional claims. Your attorney will tell you to not discuss the case and this is good LEGAL advice but not good psychological advice. You can discuss many aspects of what you are going through without discussing the clinical details of the case.

Coping with Litigation Stress

7. Take steps to restore life-work balance. Most doctors tend towards workaholism. The litigation process is uneven: one week you will feel strong and confident, the next week you may be plagued by doubts and low self-esteem. By engaging in activities that even out your life and over which you have some control ("treat the symptoms") you will feel more in control of both your personal and professional lives.

Coping with Litigation Stress

8. Actively participate in your defense. Every call to an attorney costs money, **but it is not your money**; that is why you have malpractice insurance.

Coping with Litigation Stress

9. Change the perception of the event.

- Other professionals are able to take a more unemotional view because they see this as being about business, not personal.
- It is difficult, if not impossible, for physicians to not take a patient injury personally.
- View the litigation process separately from the medical event, understand that the litigation process is just about money, and you may be able to change your perception of the event and reduce your emotional imbalance.

What has changed?

- If stress is the body reacting to the mind sensing a "fight or flight" situation, and…
- …if "fight or flight" usually indicates a loss of control or feelings of not being in control…
- …what has changed?

What has changed?

- **Fewer independent practices**
- **Movement to malpractice insurance being a line item on the profit and loss sheet**
- **Loss of consent-to-settle**
- **EMR-driven practice protocols**
- **Less time with patients**
- **Fewer "normal patients"**
- **Less "laying on of hands"**

Loss of Control

Conclusion

- Stress is simply responding to the world around you.
- Distress is an ongoing negative reaction that triggers the "fight or flight" mechanism.
- Distress is usually related to something either outside of our **control** or perceived as being outside of our **control**.
- Treat stress by treating the symptoms.
- Work to change the perception of the event.
- Take steps to gain as much control as possible.

Conclusion

- Litigation stress is a strong, sometimes crippling reaction to a medical/dental malpractice claim.
- Other professionals are able to take a more unemotional view because they see this as being about business, not personal.
- Treat the symptoms.
- Failure to deal adequately with litigation stress can result in a doctor being a bad witness on his or her own behalf, alter behavior that leads to additional claims, damage or destroy personal relationships, and even end a career.

Conclusion

A doctor should access every resource available to help deal with the stress of litigation, to include:

- Malpractice insurance company
- Local medical society
- Professional help
- Exercise
- Meditation, yoga, and/or neuromuscular relaxation
- Gain knowledge about the litigation process
- Include family

What has changed?

- If stress is the body reacting to the mind sensing a "fight or flight" situation, and…
- …if "fight or flight" usually indicates a loss of control or feelings of not being in control…
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What has changed?

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Loss of Control

SELF EVALUATION

Understanding Insurance Gaps and Managing Litigation Stress

1. Cybercrime involves unlawful acts where a computer is either a tool, a target, or both and includes such acts as:

a. Intellectual property theft.
b. Theft of information.
c. Ransomware attacks.
d. All of the above.

2. Long-term disability insurance:

a. Is income protection.
b. Should have an Any Occupation definition of disability.
c. Will replace 100% of pre-disability income.
d. Only covers catastrophic injuries.

3. The General Adaption Syndrome developed by Hans Selye:

a. Is a physical response to a perceived threat.
b. Occurs when one has control of a situation.
c. Is a very useful response today.
d. All of the above.

4. T/F – Having a gap in insurance can only hurt you professionally, not personally.

5. Distress can be described as:

a. Responding appropriately to the world around you.
b. Having a positive response to an upcoming event.
c. Having an extreme physical and emotional response.
d. An event that causes a stress response.

Answer Key: 1. D, 2. A, 3. A, 4. F, 5. C

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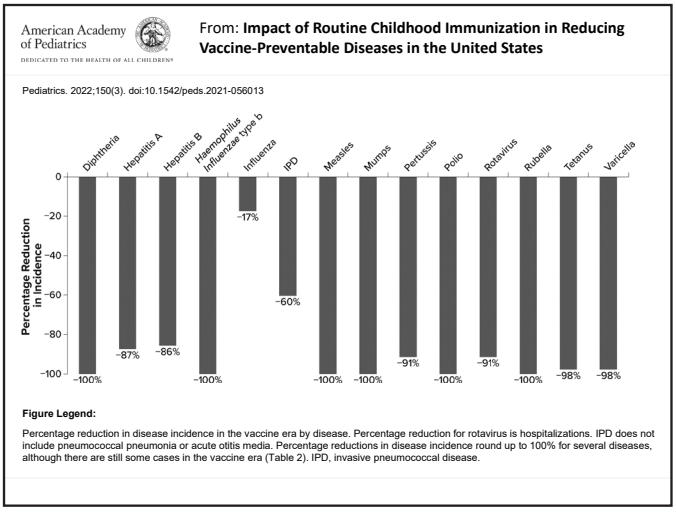
Current Pediatric Vaccination Schedules and their Impact



Vaccination Coverage by Age 24 Months Among Children Born in 2018

Number of Doses	Vaccine Type	National Immunization Survey (NIS) Immunization Rates, 2018
		United States
4	DTaP	82.3
3	Polio	93.9
1	MMR	92.8
3-4[FS*]	Hib	81.4
3	Hep B	94.8
1	Var	91.9
4	PCV	83.8

As a **complete series**: 4:3:1:3:3:1:4 = **United States** (71.3%)

*FS = Full series Hib: ≥3 or ≥4 doses of Hib vaccine depending on product type (4313314: 4 DTaP, 3 Polio, 1 MMR, 3 Hib, 3 Hep B, 1 Varicella, 4 PCV)

ChildVaxView Interactive Child Vaccination Coverage | CDC

Glass Half Full or Half Empty

No decline noted in overall routine vaccines associated with pandemic

Nationally, more than 9 in 10 young children are receiving recommended vaccines

Most children receive State required vaccines for kindergarten entry

Declines noted in children living in poverty and rural areas during pandemic

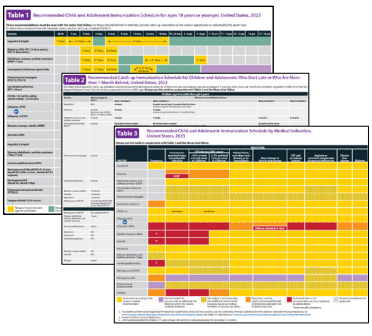
Coverage not uniform with lower rates in Black and Hispanic children, lower SES, Rural areas

Pockets of susceptibility to outbreaks exist especially in areas with higher waiver rates

CDC MMWR January 13, 2023

How Do We Improve Pediatric Vaccine Preventable Disease (VPD) Protection?

Follow The Recommendations On Time, Every Time!



- Immunization schedules for those birth through 18 years of age
  - Schedule by Vaccine and Age Group
  - Catch-Up Schedule
  - Schedule by Medical Indication
- Schedule notes include information on risk groups, minimum and recommended intervals
- Each February, CDC publishes updated child/adolescent immunization schedules

2023 Centers for Disease Control (CDC) Child and Adolescent Immunization Schedule

Standards for Pediatric Immunization Practice

- **Assess** immunization status at every visit
- **Educate** parents and guardians about recommended vaccines
- **Strong** recommendation to follow the schedule
- Offer **all recommended vaccines** at every visit
  - Follow true contraindications-do not miss opportunities
  - Administering all needed vaccines at the visit
- **Document** administered vaccines in EHR/State Registry

Based on the "Standards for Pediatric Immunization Practice"

Rotavirus Vaccine

- Routine vaccination of all infants without a contraindication
  - 2-dose series for Rotarix®(RV1) vaccine (at age 2 and 4 months)
  - 3-dose series for RotaTeq®(RV5) vaccine (at age 2, 4, and 6 months)
  - Drops given orally, live attenuated virus
- For both rotavirus vaccines
  - Minimum age for first dose is 6 weeks/Minimum Interval 4 weeks
  - Maximum age for first dose is 14 weeks 6 days/Maximum for any dose 8 mos
- Both currently licensed Rotavirus vaccines are associated with a small risk of intussusception
  - Additional risk with vaccine: 1 excess case in 20,000 to 100,000 vaccinated infants[1]
- CDC continues to recommend Rotavirus vaccination
- Greatly reduces risk (~90%) of hospitalization from diarrhea/dehydration

[1]Rotavirus Vaccine Safety

Hepatitis A Vaccine

- Recommended for all children beginning at age 12 months
- Catch-Up children aged 2-18 years without 2 valid doses of Hep A vaccine
  - Supported through the VFC program for eligible children
- Infants 6-11 months traveling outside the United States to an area where Hepatitis A vaccine is recommended, should be vaccinated
  - This dose does not count towards the routine 2 dose series
  - The routine 2-dose series should be initiated at age 12 months

Routine Schedule: 2 doses beginning at age 12 months
Minimum interval: Between dose 1 & 2 is 6 **calendar** months

Hib Vaccine

- HIB disease was the leading cause of invasive bacterial diseases in children less than age 5 years (pre-vaccine)
  - Since the vaccine, we have seen > 99% decrease in invasive disease in children < 5 years of age
- **For Best Protection Follow the Recommended Schedule**

If all doses are:	Recommended Schedule is:
ActHIB®, Hiberix®, Pentacel® (DTaP-IPV/Hib), or Vaxelis® (DTaP-IPV-HIB-HepB)	Give IM, 4 doses 3-dose Primary Series at 2, 4, 6 months Booster dose at 12-15 months*
PedvaxHib®	Give IM, 3 doses 2-dose Primary Series at 2, 4 months Booster dose at 12-15 months*

***Vaxelis should not be used for the booster dose**
- Hib vaccine is not routinely recommended after 59 months (5th birthday)

Pertussis Challenges

- Pertussis disease in US

Cases	Deaths
2021: 1609	4
2020: 5398	7
2019: 18,617	7
2018: 15,609	5
2017: 18,975	13

Photo Courtesy of Franny Strong Foundation
Francesca Marie McNally Lost Her Life to Pertussis in May 2012: frannystrong.org/

- Infants are at greatest risk for pertussis and its complications
  - 50% of infants < 1 year will be hospitalized
    - 1 out of 100 infants needing hospital treatment will die
- Vaccination is considered the best option for protection

CDC Pertussis Frequently Asked Questions

Strategies for Protecting Infants

- Vaccination during pregnancy
  - **Should receive 1 dose of Tdap during every pregnancy**
    - Preferably during the **early part** of gestational weeks 27 through 36
    - Will best ensure maternal antibody transfer to the fetus
  - If Tdap was **not** administered anytime **prior to or during** pregnancy, give Tdap immediately postpartum (not optimal)
- Study reported that vaccination with Tdap during the 3rd trimester prevented more than 3 out of 4 cases of whooping cough in babies less than 2 mos. old
- "Cocoon" the infant
  - All adults and adolescents at least 11 years old who have not previously received a Tdap vaccination, should be vaccinated at least 2 weeks before coming into close contact with a newborn (i.e., father, siblings, grandparents, caregivers)

New Study Shows Tdap Vaccination During Pregnancy can Prevent Whooping Cough in Babies

Tetanus, diphtheria and pertussis (Tdap)

- Routinely given at age 11-12 years
- Vaccinate all persons aged 13 years & older without a previous documented dose of Tdap
  - To ensure continued protection against tetanus and diphtheria, booster doses of either Td or Tdap should be administered every 10 years throughout life
- 2019 National adult immunization rates
  - Age 18 years and older: 43.6%*
- To ensure pertussis protection, Tdap can be administered regardless of interval since last tetanus or diphtheria-toxoid containing vaccine

*AdultVaxView | General Population Reports | Vaccination Coverage | CDC

Hepatitis B Vaccine (HepB)

Routine Schedule:

- Give first dose **within 24 hours of birth** to healthy babies born to HBsAg (hepatitis B surface antigen) negative moms
- 3 doses: birth, 1-2 months, and 6-12 months
- Administration of 4 doses is permitted when a combination vaccine containing HepB is used after the birth dose
- Do Not have to restart a valid series (no maximum interval)

General Best Practice Guidelines for Immunization/Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)

Hepatitis B Vaccine: Giving the Birth Dose

- For infants, whose mother is **HBsAg positive**, give hepatitis B vaccine and HBIG (hepatitis B immunoglobulin) within 12 hours of birth
- For mothers, whose HBsAg **status is unknown**:
  - Test mother ASAP for HBsAg
  - Give infant hepatitis B vaccine within 12 hours of birth
- Without postexposure prophylaxis, approximately 40% of infants born to HBV-infected mothers in the United States will develop chronic HBV infection, approximately one-fourth of whom will eventually die from chronic liver disease.

Polio Vaccine (IPV and OPV)

Routine Schedule for IPV:

4 doses given at 2, 4, 6-18 months and 4-6 years

- Oral Poliovirus Vaccine (OPV) has not been used in the U.S. since 2000
- If patient has documentation of OPV doses outside of the U.S.
  - Doses of OPV given before April 1, 2016, can be considered trivalent oral polio vaccine (tOPV) or IPV (injectable polio vaccine) and count towards doses on the U.S. schedule
  - Doses of OPV given on/after April 1, 2016 (outside the United States) are likely to be bivalent OPV (bOPV) or monovalent OPV (mOPV) and should not be counted towards a complete polio series for persons less than age 18 years
    - Repeat the invalid doses using IPV

Errata: Vol. 66, No. 1 MMWR February 17, 2017/66(6)

Pneumococcal Vaccines

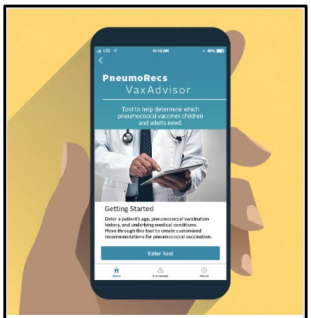
- There are 2 types of Pneumococcal Vaccines in the U.S.:
  - Pneumococcal Conjugate Vaccines (PCV13, PCV15, PCV20)
  - Pneumococcal Polysaccharide (PPSV23)
- Recommendations are based on age and medical condition
- **Children Younger Than 2 Years:**
  - Give 1 dose PCV13/15 at 2, 4, 6, and 12-15 months
- **Catch-Up Vaccination for Healthy 2 through 4 Year Old's:**
  - 1 dose PCV13/15 with any incomplete PCV series
  - For other catch-up guidance, see CDC's job aide: Pneumococcal Conjugate Vaccine (PCV)-Catch-up Guidance for Healthy Children 4 months through 4 years of Age (cdc.gov)

Pneumococcal Vaccines for Children with Certain Medical Conditions

Medical Condition	PPSV23
CSF Leak, Cochlear Implant, Chronic Heart, Chronic Lung, Diabetes	• 1 dose of PPSV23 at least 8 weeks after the PCV series is complete
Chronic Renal Failure, Nephrotic Syndrome, Congenital Immunodeficiency, Functional or Anatomic Asplenia, HIV, Sickle Cell, and Diseases treated with immunosuppressive drugs or radiation therapy	• 2 doses of PPSV23 after the PCV13 series is complete. Give the first dose at least 8 weeks after any prior PCV dose, then give the second dose of PPSV23 at least 5 years after the first PPSV23 dose

Recommended Child and Adolescent Immunization Schedule (cdc.gov)

Pneumo Recs VaxAdvisor Mobile App for Providers



PneumoRecs VaxAdvisor is available for download on iOS and Android mobile devices.

- Quickly and easily determine which pneumococcal vaccines a patient needs and when
- Incorporates recommendations for all ages so internists, family physicians, pediatricians, nurses and pharmacists alike will find the tool beneficial
- Desktop Version also available

PneumoRecs VaxAdvisor: Vaccine Provider App | CDC

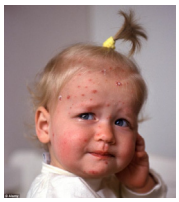
Measles, Mumps, Rubella (MMR)

- Routinely given at ages 12-15 months & 4-6 years (SC or IM)
  - Attenuated Live Virus Vaccine (CI immunosuppressed)
  - 1 extra dose of MMR vaccine at age 6-11 months if traveling to/living in endemic areas
  - Catch-up all school-aged children and adolescents without history of 2 doses of MMR
- Persons **previously vaccinated** with 2 doses of a mumps virus containing vaccine who are identified by public health authorities as being part of a mumps outbreak should receive a third dose of a mumps-virus containing vaccine (MMR)

Recommendation of the Advisory Committee on Immunization Practices for Use of a Third Dose of Mumps Virus-Containing Vaccine in Persons at Increased Risk for Mumps During an Outbreak

Varicella

- Routine Schedule: 1st dose at 12-15 months of age; 2nd dose 4-6yrs (SC or IM)
- Varicella is attenuated live virus – CI in immunosuppressed
- Minimum intervals between doses vary by age:
  - Children 12 mo.- 12 yr. 3 months between doses
  - Persons 13 yr. & older: 4 weeks between doses



Meningococcal Disease

- Serogroup B and C are the major causes of meningococcal disease in the U.S.
  - Each responsible for approximately 25-40% of cases
- Proportion of U.S. serogroup disease varies by age group
  - B: 60% of disease among children and young adults under 24 years of age
    - College students have more than 3X the risk of serogroup B as similarly aged people not attending college
  - C, Y, W-135: 60% of all cases of meningococcal disease among persons 24 years of age and older
- Overall case fatality of meningococcal disease is 10-15% even with appropriate antimicrobial therapy
  - Can be even higher in persons with meningococcemia
- Approximately 20% of survivors have permanent sequelae such as: hearing loss, neurological damage, or loss of limb

Pinkbook Course Book: Epidemiology of Vaccine Preventable Diseases | CDC

Meningococcal Conjugate Vaccine (MenACWY)

- For best protection, follow the recommended schedule
  - **Give IM, 2 doses at ages 11-12 years & 16 years**
    - Minimum interval between 2 doses is 8 weeks
    - If 1st dose is given at age 16 years or older, a 2nd dose is not needed
  - Ensure first year college students living in residential housing have received a dose of MenACWY at 16 years or older
  - Not routinely recommended for healthy persons aged 22 years and older
  - Targeted risk groups (i.e. asplenic)may receive as young as age 2 months and get booster q3-5 years based on age, indications

http://immunize.org/catg.d/p2018.pdf

ACIP Meningococcal Vaccine Recommendations | CDC

Meningococcal B Vaccine

- Administer to persons aged 10 years and older
  - With persistent terminal complement component deficiency
  - With asplenia (anatomic or functional)
  - Who are taking a complement inhibitor such as Soliris® or Ultomiris®
  - Who are exposed during a community outbreak
  - Who are microbiologists exposed to *N. Meningitides*
- Based on shared clinical decision making, persons aged 16-23 not in a high-risk group, may be vaccinated
  - Providers need to discuss risks and benefits with these persons
  - Series preferably given at ages 16-18 years

Meningococcal Vaccination for Adolescents: Information for Healthcare Professionals

Meningococcal B (MenB)

- Meningococcal B Vaccines
  - Bexsero (Novartis) 2 doses at least 4 weeks apart
  - Trumenba (Pfizer) 2 doses at 0, 6 months **or** 3 doses at 0, 2, 6 months[1]
- **Same brand** must be used to complete the series
- MenACWY and MenB vaccines may be given at same visit
- For those with risk factors give a booster 1 year after primary series then q2-3 years

[1]Young adults aged 16 through 23 years who are healthy and not at increased risk for MenB disease may receive a 2-dose series of Trumenba at 0 & 6 months for short term protection against most strains of MenB disease. **All other persons are recommended to receive a 3-dose series, including those in an outbreak.** This is found in the notes of the 2023 Children and Adolescent Immunization Schedule

HPV Infection

- By age 50, at least 4 out of every 5 (at least 80%) women will have been infected with HPV at one point in their lives. HPV is also very common in men[1]
  - More than 42 million Americans are currently infected with HPV types that cause disease
  - About 13 million Americans become infected each year
  - HPV infection is most common in people in their late teens and early 20s
- Easily spread by intimate skin-to-skin contact during sexual activity
  - Not just with sexual intercourse
- Most people will never know they have been infected

[1]Basic Information about HPV and Cancer
CDC Basic Genital HPV Infection-Fact Sheet
HPV Infection | Human Papillomavirus (HPV) | CDC

HPV-Attributable Cancers

- Annually in the U.S., an average of 46,143 new cases of cancer occur in parts of the body where mucosal HPV types are found*
  - Cervix, vagina, vulva
  - Anus, penis
  - Oropharynx
- Of these, about 33,700 attributed to HPV types that are preventable with the 9-valent HPV vaccine
- Study finds high burden of oral HPV related cancers in men
  - 1 in 9 men are infected with HPV
  - Cancer causing strains of HPV were more common in men
    - Highest risk type (HPV 16) was six times more common in men

* Based on Data from 2014 to 2018

HPV-Associated Cancer Statistics
United States Cancer Statistics Data Brief No.26 December 2021
CIDRAP-Study Finds High Burden of Oral HPV Related Cancers in Men

HPV Vaccine Points

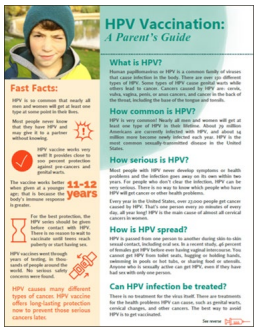
9vHPV Serotypes:	6, 11, 16, 18, 31, 33, 45, 52, 58
Protection Against:	Cervical, vaginal, vulvar, penile, anal, oropharyngeal cancers; genital warts; precancerous or dysplastic lesions
Licensed for Ages:	9 through 45 years
Routine Age:	Age 11-12 years
Catch-Up Age:	Males and Females through 26 years of age
Adults 27-45:	Shared clinical decision-making[1]

- For persons who initiate an HPV series prior to their 15th birthday: 2-dose HPV schedule (0, 6-12 months)
- For persons who initiate HPV series at/after age 15 years and for persons who are immunocompromised (regardless of age at 1st dose): 3-dose schedule (0, 1-2, 6 months)

[1]HPV vaccine may benefit some adults aged 27 through 45 years who are not adequately vaccinated. Providers, through shared clinical decision, can discuss HPV vaccination with persons who are most likely to benefit.

Why At Age 11 or 12 Years?

- HPV vaccine works best when the entire series has been given before exposure to HPV
- Youth Behavioral Risk Surveillance:
  - 27.4% 9th-12th graders reported being sexually active
    - 7% had sexual intercourse before age 13
    - 26.9% had sexual intercourse with 4 or more persons during their lifetime
    - 20.5% had sexual intercourse with 2 or more persons in the previous 3 months



Youth Risk Behavior Surveillance — United States, 2019 (cdc.gov)

Influenza Vaccine: Everyone, Every Year

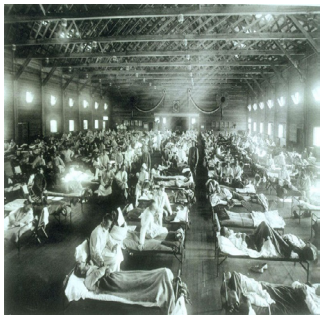


Photo Courtesy of the National Museum of Health and Medicine

- Recommended for all person's aged 6 months and older!
- Vaccinate close contacts of those at high risk to provide another layer of protection including
  - Health Care Personnel (HCP)
  - Parents of infants less than 6 months of age
- Continue to ensure that persons at higher risk for influenza related complications are vaccinated
- With the exception of adults 65 years and older, there is no preferential recommendation for one flu vaccine product over another

A Look at IIV4

IIV4
Flu Strains: 2 A, 2 B
Product Type: Standard-dose (SD), unadjuvanted
Age Indication: 6 months and older
Route: IM (Intramuscularly)
For persons who are healthy, have any underlying medical conditions, or who are pregnant

Inactivated influenza vaccines labeled for IM administration **must** be given IM; if not dose must be repeated.

A Look at LAIV4

LAIV4 (FluMist® Quadrivalent)
Flu Strains: 2 A, 2 B
Route: Administered intranasally (IN/NAS)
Age Indication: 2-49 years (healthy, not pregnant)

Do not miss an opportunity to vaccinate, use any age-appropriate flu vaccine that is available

COVID-19 Vaccine Clinical Considerations

- Both Moderna and Pfizer mRNA vaccines authorized for use in children for primary and booster doses
- There are differences with age indication, dosing, schedule, and storage and handling

COVID-19 Vaccination Clinical Resources

Coadministration

- COVID-19 vaccines **may be administered without regard to timing of other vaccines**
- This includes simultaneous administration of COVID-19 vaccine and other vaccines on the same day
- If multiple vaccines are administered at a single visit, administer each injection in a different injection site
- Best practices for multiple injections include:
  - Separate injection sites by 1 inch or more, if possible
  - Administer the COVID-19 vaccine and vaccines that may be more likely to cause a local reaction in different limbs, if possible

Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC

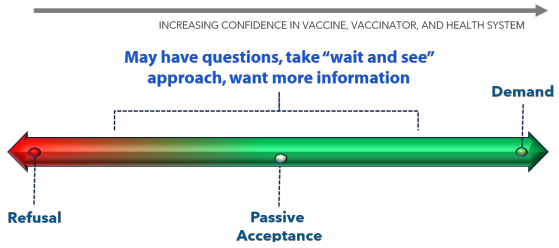
Oops - Common Administration Errors

- DTaP and Tdap
- Live/Live: either at same time or separated by 28 days
- Adult vs Peds Hep A or B – different dosages
- Reconstitution errors – must use the diluent that comes with it
- IM vs SC – MMR and Varicella now can be given IM or SC
- Minimum intervals must be met, or dose repeated

Promoting Vaccine Confidence Through Vaccine Conversations

Starting the Vaccine Conversation

Willingness to Accept a Vaccine Falls on a Continuum



Hesitancy Versus Refusal

- Those that fall in the middle are often referred to as Fence-sitters
  - They have questions and just want to know more about vaccines
- Fence-sitters versus anti-vaccinators
  - Not likely to convince the anti-vaccinator
- A focus on educating fence-sitters will be more beneficial than trying to persuade those who completely oppose vaccines
- Is complex and context specific varying across time, place, and vaccines
- Is influenced by factors such as complacency, convenience, and confidence

Victims of Their Own Success

- One of the greatest public health achievements 20th century
- Many physicians have not seen cases of VPDs
- Parents are a generation or more removed from smallpox, polio, rubella, and other serious VPDs
  - Because of this, VPDs are felt by some to be a harmless right of passage for children and less dangerous than vaccination

Impact of Vaccines in the 20th & 21st Centuries

Comparison of 20th Century Annual Morbidity & Current Morbidity: Vaccine-Preventable Diseases

Disease	20th Century Annual Morbidity*	2017 Reported Cases†	% Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Pertussis	200,752	18,975	91%
Tetanus	580	33	94%
Polio (paralytic)	16,316	0	100%
Measles	530,217	120	>99%
Mumps	162,344	6,109	96%
Rubella	47,745	7	>99%
CRS	152	5	97%
Haemophilus influenzae	20,000 (est.)	33§	>99%

* *JAMA*. 2007;298(18):2155-2163

† CDC. *National Notifiable Diseases Surveillance System, 2017 Annual Tables of Infectious Disease Data*. Atlanta, GA. CDC Division of Health Informatics and Surveillance, 2018. Available at: www.cdc.gov/nndss/infectious-tables.html. Accessed on December 3, 2018. NNDSS finalized annual data as of November 28, 2018.

§ *Haemophilus influenzae* type b (Hib) <5 years of age. An additional 10 cases of Hib are estimated to have occurred among the 203 notifications of Hi (<5 years of age) with unknown serotype.

What's the Risk?

As vaccine preventable diseases recede from memory…

the perceived benefit of vaccines and risk of disease become less clear.

What Influences Vaccine Confidence

- Parents/patients are strongly influenced by other parents/individuals and what they read
- Often through social media and news sources
- Parents/patients express concerns about the safety
  - Ingredients, too many vaccines at one visit, and not properly tested
- Parents/patients consider vaccines to be ineffective
- Parents/patients don't see disease as a risk
  - Susceptibility to disease and severity of disease

Resource: Ropeik, David, How Risky Is It, Really?: Why Our Fears Don't Always Match the Facts, 2010

James Gillray (British, 1756-1815), The cow-pock,-or-The wonderful effects of the new inoculation! - Vide - the Publications of ye AntiVaccine Society, 1802. Hand colored etching with aquatint. Bequest of Gordon N. Ray, 1987; 1986.319. Morgan Museum New York.

220 Years Later

the only thing that's changed is how quickly information spreads

Vaccine Conversations

- Answering questions can be challenging
  - Staff is not always prepared for questions
  - Inconsistent messages from staff
  - Real-life time constraints
  - Frustrating! Correcting misconceptions can successfully reduce misperceptions, but does not always result in vaccination

Image Courtesy of CDC

What You Say Matters

- Research shows a patient who receives a **strong recommendation** from a provider is 4-5 times more likely to be vaccinated
- **Personalizing** the message that vaccines are safe and effective can be powerful
  - Patients often are more likely to be persuaded by stories and anecdotes about the successes of vaccines

What You Say AND How You Say It Matters

- The best predictor of vaccination is how the provider started the conversation
  - For both vaccine hesitant and non-hesitant patients
- Good recommendation = simple, strong and personalized
  - "It's time for John's flu shot. I recommend he get vaccinated today. I get vaccinated and my children do too. It's the healthy thing to do." (Presumptive approach)

VERSUS

  - "Research suggests that persons vaccinated with influenza vaccine have a decreased chance of contracting disease and complications associated with influenza. Would you like John to get vaccinated today?" (Participatory approach)

Use a Whole Team Approach to Vaccination

- ALL staff play a role in vaccine communication
  - From the front to the back of the office
- Healthcare providers who feel confident in vaccines are more likely to recommend them to patients
- Ensure staff has access to:
  - Up-to-date information on vaccine recommendations
  - Access to clinical resources and trainings on vaccination
  - Answers to their own questions about vaccines

SELF EVALUATION

Current Pediatric Vaccination Schedules and their Impact

1. Best practices for health professionals who administer vaccines include which of the following?

a. Assess immunization status at every office visit
b. Educate parents about recommended vaccines
c. Strong provider recommendation
d. Offer all recommended vaccines at every visit
e. All of the above

2. T/F - Pregnant women should receive an additional dose of Tdap during every pregnancy.

3. An 11 year old seen in your office is noted to have received 2 prior doses of Hepatitis B vaccine, at age 2 months and age 5 years. To complete the series it is routinely recommended to:

a. Give a third and final dose to complete the series
b. Restart the series and give 3 doses of HBV at 0,1, and 6 months
c. Check a titer for immunity to Hepatitis B and give a booster dose if nonimmune

4. T/F - Hepatitis A Vaccine is recommended only for children with underlying medical conditions or who are travelling to an area with endemic disease.

5. Children over two years of age with which underlying medical conditions should receive PPSV23 in addition to completing the Pneumococcal Conjugate Vaccine series?

a. Chronic Heart Disease or Chronic Lung Disease (excluding asthma)
b. Diabetes or Kidney disease
c. Immunodeficiency
d. All of the above

6. HPV Vaccine protects males against which of the following

a. Anal Cancer
b. Oropharyngeal cancer
c. Genital warts
d. All of the above

7. T/F - A child is seen in the office for their 4 year old immunization visit. It is noted that MMR, Varicella Vaccine, DtaP, and Polio vaccine are due, but 2 weeks prior to today's visit they received a flu shot at a local pharmacy. You should recommend waiting until 4 weeks after the inactivated flu vaccine to get further immunizations.

Answer Key: 1. E, 2. T, 3. A, 4. F, 5. D, 6. D, 7. F

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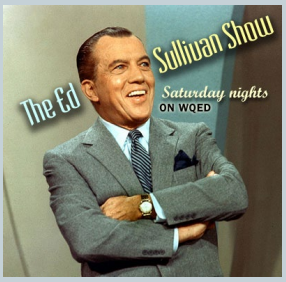
Sexual Health in the Elderly Patient Population

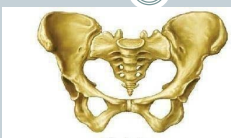
I have nothing to disclose

Except…A "few" of my slides MIGHT be "sexual" in nature….

September 9, 1956

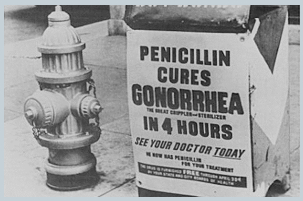


Elvis the Pelvis


Pelvis


Pelvis Presley

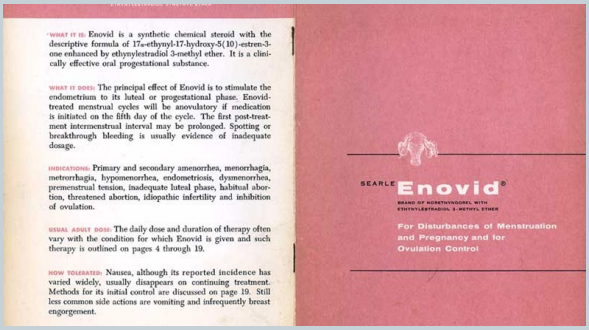
Sexual Revolution 1960



Sexual Revolution

End of World War 2, Feminism

Physician's Pamphlet for The Pill



Masters and Johnson

Masters and Johnson

- the first laboratory data on the anatomy and physiology of human sexual response based on direct observation
- *Human Sexual Response* and *Human Sexual Inadequacy*
- They identified four physiologic stages of
- the sexual response: 1) excitement, 2) plateau, 3) orgasm, and 4) resolution

Diagnostic and Statistical Manual of Mental Disorders (DSM) Diagnoses

- Types of Sexual Dysfunction
  - sexual desire disorder
  - sexual arousal disorder
  - orgasmic disorder
  - sexual pain disorder

OUR AGING SOCIETY - THE REALITY

- "During the 20th century, the average lifespan in the United States increased by more than 30 years; 25 years of which can be attributed to advances in public health."
- Currently, approximately 12% of U.S. population ≥65 years old
- An estimated 5% of people age 65 and 20% of those over 85 will spend time in a long term care facility

Intimacy in the Assisted and Long Term Care facility

- What other factors come into play in these setting(s)?
  - Dementia
  - Frailty
  - Staff attitudes
  - Family attitudes
  - Liability

Sex and Sexuality: Nature vs. Culture

- What is sex?
  - How do we define sex or sexual activity in the U.S. in 2010?
- What is sexuality?
  - How do men, women express their sexuality?
  - Does age affect expressions of sexuality?
- What is sexy?
  - How do we, as a culture, create standards through which our perceptions are shaped as to who or what is attractive or desirable?

Sexuality and Images of Health: Is there a connection?

Sexuality and Images of Health: Is there a connection?

Sex and our Aging Bodies and Minds

- What changes are normal?
- What can we attribute to the "typical" aging process?
- What changes are abnormal?
- What changes are indications of physiological pathology?

PHYSIOLOGY AND PSYCHOLOGY OF AGING: IMPACT ON SEXUAL HEALTH AND SEXUAL EXPRESSION

- Women
  - Peri and Post-Menopausal changes:
    - Peri-menopause: early/mid forties onset for most women including hot flashes, lack of sleep, irritability, depression
    - Post-menopause: lack of estrogen causes thinning vaginal walls, decreased elasticity, the vagina shortens and narrows, and decreased lubrication during sexual arousal
  - Other Health Issues:
    - Chronic pain, hysterectomy, mastectomy, HTN, diabetes, arthritis
  - Psychosocial stressors:
    - Family, Work, Stress, Depression, Sexual Trauma

PHYSIOLOGY AND PSYCHOLOGY OF AGING: IMPACT ON SEXUAL HEALTH AND SEXUAL EXPRESSION

- Men
  - Erectile Dysfunction (ED):
    - Up to 50% of men 50-69 years old and 70% of men ages 70 years and older are affected by ED.
    - HTN, diabetes, BPH and s/p prostatectomy, insufficient testosterone, chronic pain, medications (beta blockers)
  - Other Health Issues w/out ED as a component:
    - HTN, chronic pain, arthritis, COPD, diabetes,
  - Psychosocial stressors:
    - Family, Work, Stress, Depression (men less likely to discuss this)

The Health Care Provider (HCP) Sex and older Adults

- How do our perceptions impact on our practice as HCPs for the older adult patient?
  - What do you think of when you viewed these pictures?
  - What health issues would you have on your mental list of "things to address"?

BARRIERS IN THE HEALTH CARE SETTING

Health Care Provider

- Discomfort and/or embarrassment
- Minimal topic-specific education
- Lack of time requiring "prioritizing" of health issues that "matter more"
- The Medical Model focuses on dysfunction of a system
- Sexuality and sex are more than just the penis and vagina

BARRIERS IN THE HEALTH CARE SETTING

Patient

- Discomfort and/or embarrassment
- Personal beliefs
- Lack of knowledge
- Community vs. Long Term Care dwelling

Declaration of Sexual Rights

- International organizations have recognized and demanded sexual rights as universal rights based on inherent freedom, dignity and equality of all human beings
- Older adults shall have rights to:
  - Access the highest attainable standard of sexual health
  - Access to sexual education
  - Decision to be sexually active or not

Treatments for Male Sexual Dysfunction

- Not focus of this lecture

However…

March 27, 1988

Sildenafil

- Potent and selective inhibitor of cGMP phosphodiesterase (PDE5)
- First oral treatment approved to treat erectile dysfunction in the United States
- When taken by mouth sildenafil for erectile dysfunction results in an average time to onset of erections of 27 minutes

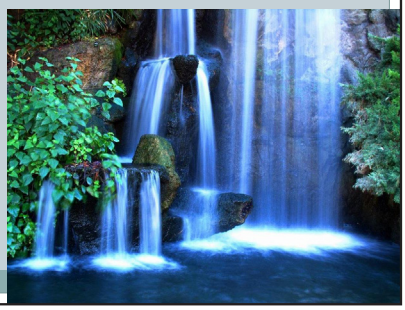
$1.93 Billion

Treatments for Female Sexual Dysfunction

- Lubricants
- Vaginal Estrogen (not covered in this lecture)
  - Estradiol tablets, creams
- Vaginal Dilators
- Pelvic Floor Physical Therapy
- Relaxation techniques and Yoga
- Diet and Exercise
- Flibanserin?

Lubricants

- Water based
- Oil based
- Silicone based
- Organic based
- Risks



Vaginal Dilators

- an instrument used to gently stretch the vagina when it has become narrowed vaginal stenosis

Pelvic Floor Physical Therapy

- Manual Therapy
- Pelvic floor electromyography (EMG), a biofeedback instrument
  - measures muscle activity

Diet, Exercise, Yoga

- Women who are a normal Body Mass Index, and exercise on a daily basis experience the symptoms of menopause with greater ease
- Yoga relaxation

August 2015
"Add Your Interest"

Flibanserin

- Flibanserin, sold under the trade name "Add Your Interest", is a medication approved in 2015 by the FDA for the treatment of pre-menopausal women with hypoactive sexual desire disorder (HSDD).
- The medication increases the number of satisfying sexual events per month by about one half to one over placebo from a starting point of about two to three. The certainty of the estimate is low

Is Flibanserin the new "Female Sildenafil?"

Summary

- It is important to understand the events of the sexual revolution
- Addressing sexuality and intimacy is an important job of the healthcare provider
- There are several natural methods available to treat female sexual dysfunction

SELF EVALUATION

Sexual Health in the Elderly Patient Population

True/False

1.___ The four phases of the human sexual response in order are: excitement , plateau, orgasm and resolution.

2.___ The most common type of sexual dysfunction in women is orgasmic disorder.

3.___ Menopause is considered normal to enter anytime after age 30.

4.___ Beta blockers to treat hypertension in men are a significant cause of erectile dysfunction.

5.___ An elderly adult who's considered mentally competent living in an assisted living facility is prohibited from sexual activity.

6.___ Viagra onset of action from ingestion of the medication is 3 hours.

7.___ Addyi is a medication for women approved by the FDA for the treatment of hypoactive sexual desire disorder.

Answer Key: 1. T, 2. F, 3. F, 4. T, 5. F, 6. F, 7. T

Dr. Gerald Levine, MD, CCFP

Dr. Gerald Levine, MD, CCFP (Canadian College of Family Physicians), of Barrie, Ontario, graduated from the University of Toronto Medical School and the University of Toronto Family Medicine School. He was a family practitioner for over 30 years and since 2006 has focused on stress management, burnout prevention and mindfulness facilitation offering training physicians, dentists, and their staffs as well as for dental and medical associations throughout Canada including the Simcoe Muskoka District Health Unit, the General Practitioner Psychotherapy Association of Canada, the Canadian Mental Health Association York Region and many others. Dr. Levine has also authored an e-book, *52 Mindful Weeks, Cultivating Awareness and Resilience* available on his website, www.ManageStress.ca.

You may contact Dr. Levine with you questions or comments at geraldlevine@rogers.com, or by phone at 705-721-3130.

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Communicating Effectively with Staff & Patients: Barriers and Solutions

Learning Objectives :

Identify and assess barriers to listening and communication with patients and staff

Apply self care and mindfulness skills to enhance listening and communication

Communication is only as good as the outcome!

3 things to remember:

Mindful Awareness

Self Care

60 second listening rule

Topics:

Listening/Communication Barriers

Self Care and Mindful Solutions:

Self Awareness

Self care

Mindfulness

Mindful listening

"Communication 101" for Staff/Patients

Mindful Self Compassion

Barriers to Listening

Comparing

Mind reading

Rehearsing

Filtering

Judging

Being right

Dreaming

Advising

Sparring

Derailing

Placating

Barriers to Communication:

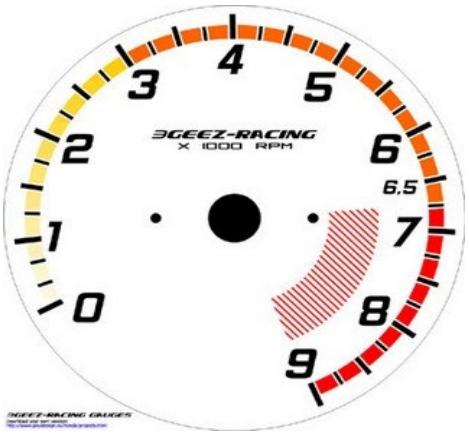
- Failing to clarify
- Not listening
- Imposing solutions
- Leading questions
- Not acknowledging others
- Making assumptions
- Avoiding honest feedback

SOLUTIONS:

Self Awareness
Self Care
Mindfulness
Mindful Listening
Communication 101
Effective Communication :Staff
Effective Communication:Patients
Managing Secondary Traumatic Stress

SOLUTIONS:
Self Awareness

Self Care
Mindfulness
Mindful Listening
Communication 101
Effective Communication :Staff
Effective Communication: Patients
Managing Secondary Traumatic Stress



Self Awareness

Internal stress o meter

Frequent “check in”

Time and space for inventory: “I'm too busy”

Recognizing your personal stress triggers

Recognizing your own stress reaction

- Cultivating ”3rd person” perspective,
- awareness of inner dialogue

SOLUTIONS:

Self Awareness
Self Care
Mindfulness
Mindful Listening
Communication 101
Effective Communication :Staff
Effective Communication: Patients
Managing Secondary Traumatic Stress

HALT !

HUNGRY?
ANXIOUS/ANGRY?
LONELY?
TIRED?

Basic self care

Common sense, but not common practice
Routine (especially during pandemic)
Sleep
Food
Exercise/fresh air
Relationships
Vacation
Hobbies/interests
Meditation/Spiritual connection

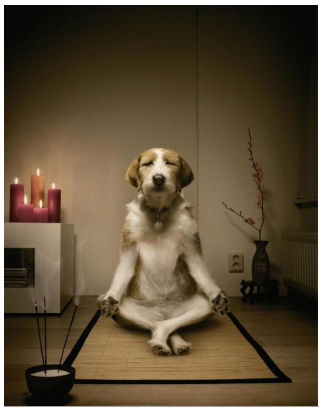
.Caffeine, alcohol, drugs, screen time, overworking….not!

SOLUTIONS:

Self Awareness
Self Care

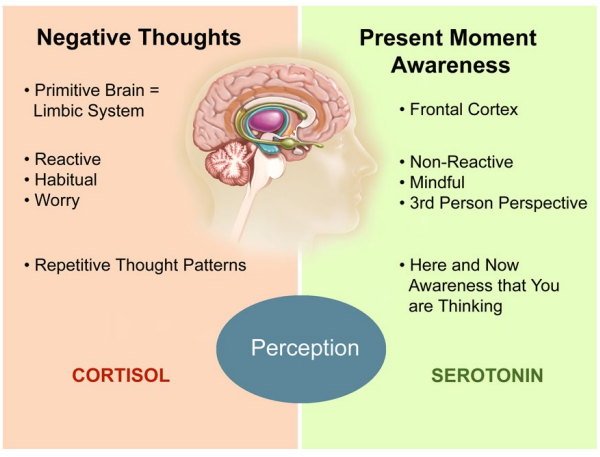
Mindfulness

Mindful Listening
Communication 101
Effective Communication: Staff
Effective Communication: Patients
Managing Secondary Traumatic Stress



Mindfulness:

- Paying attention to the here and now with attitudes of curiosity and acceptance
- Intentional focus on the present
- Repeated shifting of attention from the past or future to the present moment
- Awareness of what you are doing as you are doing it



Mindfulness :Myths and Facts

- **Myths:** trying to empty the mind, religious doctrine, passive,
- isolating, waste of time

- **Facts :** scientifically proven concentration/attention training
- rewires the brain for calm, clear problem-solving,
- wise responses, presence, connection with others

Mindful Principles/Attitudes

- Kindness
- Non-judgment
- Acceptance
- Patience
- Curiosity
- Trust
- Non-striving
- Letting go/reduced attachment

SOLUTIONS:

Self Awareness
Self Care
Mindfulness
Mindful Listening
Communication 101
Effective Communication :Staff
Effective Communication: Patients
Managing Secondary Traumatic Stress

Mindful Listening

awareness of listening blocks
being present
uni tasking
listening to understand (not necessarily agree)
body language
listening as a meditation practice

SOLUTIONS:

Self Awareness
Self Care
Mindfulness
Mindful Listening
Communication 101
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Effective Communication: Patients
Managing Secondary Traumatic Stress

Communication 101

Styles of Relating:
Aggressive
Passive
Assertive

Communication 101

4 A's
Availability
Assertiveness
Ask
Accept

Communication 101

4 F's (FREE)
Figure out
Responsibility
Express
Empathy

SOLUTIONS:

Self Awareness
Self Care
Mindfulness
Mindful Listening
Communication 101
Effective Communication: Staff
Effective Communication: Patients
Managing Secondary Traumatic Stress

Mindful Communication with Staff

Clarity
Enquire(empathic curiosity)
Hear
Acknowledge
Straight Talk

Mindful Communication with Staff

.1) Understand communication styles
.2) Aim for understanding
.3) Listen actively: BE PRESENT
.4) Be willing to compromise
.5) Avoid hurtful language
.6) Speak assertively with "I statements"
.7) Concern and respect
.8) Manage intense emotions
.9) Notice nonverbal clues
.10) Validate

SOLUTIONS:

Self Awareness
Self Care
Mindfulness
Mindful Listening
Communication 101
Effective Communication :Staff
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Managing Secondary Traumatic Stress

Mindful Communication with Patients

60 second listening rule
Patient satisfaction increased
Practitioner satisfaction increased
lawsuit reduction!

Mindful Communication with Patients

1) Centering breath, body scan, letting go of residue
2)initial question, intention to help:
"what matters most to this patient right now?"
3) allow 60 seconds or more of listening to understand
4)questions for self: "what am I ignoring/assuming?"
5)relish silences(diastole of communication)

SOLUTIONS:

Self Awareness
Self Care
Mindfulness
Mindful Listening
Communication 101
Effective Communication: Staff
Effective Communication: Patients
Managing Secondary Traumatic Stress

Managing Secondary Traumatic Stress

Secondary traumatic stress/empathy fatigue
Mindful self compassion
One for me, one for you

Managing Secondary Traumatic Stress

Mirror neurons: preverbal empathy/resonance
Secondary traumatic stress/empathy fatigue
Burnout

Managing Secondary Traumatic Stress

Mindful self compassion:

Mindful awareness vs self-absorption
Self kindness vs self critic
Common humanity vs isolation

Managing Secondary Traumatic Stress

Mindful self compassion

"This a moment of difficulty"
"One for me, one for you"
Including yourself equally in the circle of care
Treating yourself as a good friend

Communication is only as good as the outcome!

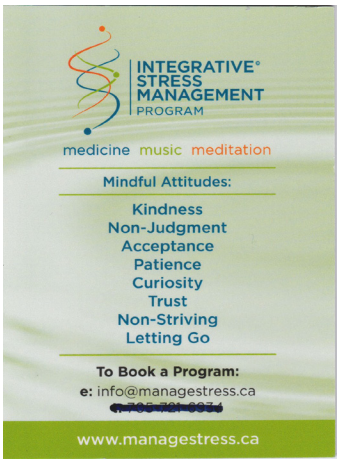
3 things to remember:

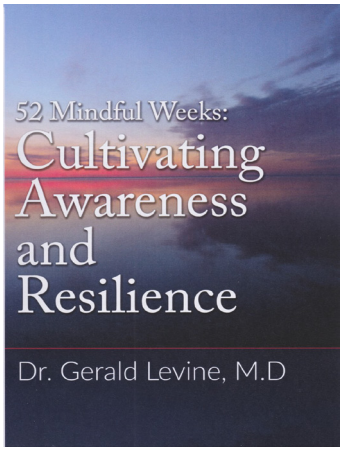
Mindful Awareness

Self Care

60 second listening rule

....thanks for listening!





CONTINUED PRACTICE/RESOURCES

Dr Gerald Levine: www.managestress.ca
ebook: 52 Mindful Weeks

Mindfulness: Full Catastrophe Living by Dr. Jon Kabat-Zinn
The Mindful Brain by Dr. Daniel J. Siegel
The Mindfulness Solution by Dr. Ronald D. Siegel
Meditation for Fidgety Skeptics by Dan Harris
Deep Listening and Communication by Dr. Ron Epstein
Communication skills: Greenline Conversations
CenterforMSC.org Dr. Kristen Neff
APPS: 10% Happier, Insight Timer, Calm, Headspace

SELF EVALUATION

Communicating Effectively with Staff & Patients: Barriers and Solutions

1. Barriers to listening include:

a. mind reading
b. comparing
c. advising
d. being right
e. filtering
f. all of the above

2. Barriers to communicating include:

a. not listening
b. making assumptions
c. avoiding honest feedback
d. imposing solutions
e. failing to clarify
f. all of the above

3. T/F - Aggressive and Assertive styles of relating are the same.

4. The FREE mnemonic includes:

a. Figure out what you need to say
b. Responsibility for your side of communication
c. Express yourself aggressively
d. Empathize with others points of view
e. all of the above
f. a,b,d

5. T/F - Mindfulness meditation requires you to empty your mind.

6. T/F - The 60 second rule makes your office day longer and less satisfying.

7. T/F - Empathy fatigue leads to burnout and poor communication.

Answer Key: 1. F, 2. F, 3. F, 4. F, 5. F, 6. F, 7. T