THE
2019-20

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
President

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 2019-20 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, dentistry, pharmacology, asset protection, revenue cycle management and practice management. And their presentations include discussions ranging from responding to medical emergencies, preventing practice embezzlement, asset protection, the defendant doctor's deposition, and practice efficiency, to newly FDA approved drugs, chronic pain management, maintaining brain fitness, dealing with personality disordered patients and prescription drug diversion..

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 form given to you by your classroom facilitator. In addition, I encourage you to contact any of our faculty members directly with questions or comments or submit your inquiries on the provided cards and we will see to it that they're forwarded promptly.

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
President

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COURSE OBJECTIVES

After completing ***The 2019-20 Medical-Dental-Legal Update*** you should have acquired the knowledge that will better enable you to:

- Understand and avoid professional practice **legal and financial risks**.
- **Protect personal and professional assets** against liability exposure.
- Utilize a variety of clinically **relevant but relatively unknown treatments**.
- Better diagnose and treat **Allergic Rhinitis**.
- More effectively screen for and treat **Hepatitis C**.
- Become more familiar with strategies to slow or **avoid cognitive decline**.
- Understand approaches to **improve both patient care and the bottom line**.
- Undertake approaches to **optimize appointment scheduling**.
- Provide better care to patients with **personality disorders**.
- Better understand and treat **chronic pain**.
- Better understand and utilize recent **type 2 diabetes** management guidelines.
- Discuss immunization updates and **new FDA drug approvals** and safety guidelines.
- Understand the scope and implications of **prescription drug abuse and diversion**.
- Better prepare for and perform at a malpractice **deposition**.
- More effectively respond to a **medical emergency** in the healthcare office.
- Help lower healthcare practice vulnerability to **embezzlement**.

All learning objectives above address IOM/ACGME core competencies.

THE 2019-20

Medical-Dental-Legal UPDATE

FACULTY DISCLOSURES

The individuals listed below have control over the content of ***The 2019-20 Medical-Dental-Legal Update***. None of them have a financial relationship with a commercial interest whose products or services are discussed in the presentation(s) over which they have control:

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Louis Kuritzky, MD

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 Family Medicine Residency Program of North Florida Regional Medical Center 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.*

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Things I Wish I Knew Last Year

Off-Label Issues

OFF-LABEL content in this presentation:

1) Zolpidem for Expressive Aphasia
2) Tranexamic Acid for Hemorrhoidal Bleeding

ASA for T2DM

Your newly 52 y.o. T2DM is otherwise healthy and in good control on metformin 1 g b.i.d. Should he take ASA for 1^0 prevention?

a) Yes. DM is a 'CV risk equivalent', thus all Rx is considered 2^0 prevention and of substantial value

b) Yes. Benefits > Risks for 1^0 prevention hypoglycemia outweigh benefits

c) No. Risks > Benefits for 1^0 prevention

d) Maybe: Risks ±= Benefits

ADA: ASA Recommendations 2019

"ASA therapy (75–162 mg/day) may be considered as a 1^0 prevention strategy in those with DM who are at ↑CV risk, after a discussion …on the benefits versus increased risk of bleeding." **C**

ADA Standards of Medical Care in Diabetes 2019
Diabetes Care 2019;42(Suppl 1):S103-S123

ADA: ASA Recommendations 2019 Just Who is Included Under " ↑ CV risk"

- Age 50 -69 years (♂ & ♀)
- At least 1 CVD RF
  - FHx Premature ASCVD
  - HTN
  - Dyslipidemia
  - Smoking
  - CKD
  - Albuminuria
- NOT at ↑Bleeding Risk

ADA Standards of Medical Care in Diabetes 2019
Diabetes Care 2019;42(Suppl 1):S103-S123

ADA: ASA Recommendations 2019 Age Limit = 70

"For patients over the age of 70 years…the balance appears to have greater risk than benefit…and may generally not be recommended."

ADA Standards of Medical Care in Diabetes 2019
Diabetes Care 2019;42(Suppl 1):S103-S123

ASPIRIN SECONDARY Prevention

"For 2^0 prevention of CVD in patients with DM, we recommend aspirin 75-162 mg/d"

McCulloch DK Overview of medical care in adults with DM UpToDate Updated 3/9/16

ASPIRIN PRIMARY Prevention

"For 1^0 prevention of CVD in patients with DM at ↑ CVD risk (10 yr risk >10%) we suggest aspirin (75-162 mg/d), although the evidence supporting this approach is weak."

McCulloch DK Overview of medical care in adults with DM UpToDate Updated 3/9/16

ASPIRIN in Diabetes

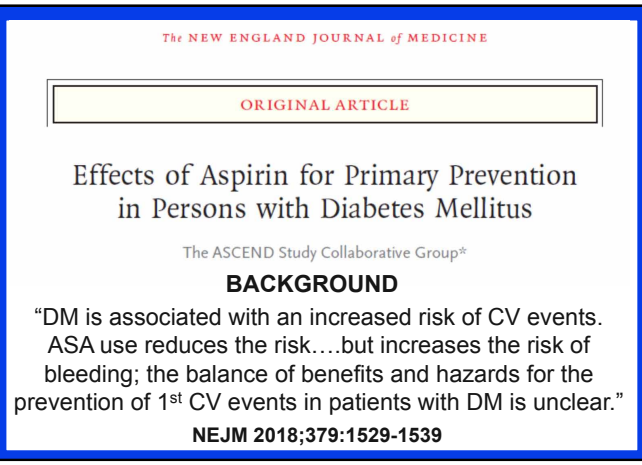
	n	f/u yrs	ASA mg/d	CV RR	p
Primary Prevention Project	1,031	3.7	100	0.9	NS
Early Rx DM Retinopathy	3,711	3-8	650	0.83	NS
POPADAD	1,276	6.7	100	0.98	NS
Japanese PPP	±5/14K	5	100	0.89	NS

McCulloch DK Overview of medical care in adults with DM UpToDate Updated 3/9/16

ASPIRIN in Diabetes: NOT

"Thus, trials in patients with diabetes do not show a significant benefit of aspirin for the primary prevention of CV events."

McCulloch DK Overview of medical care in adults with DM UpToDate Updated 3/9/16



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

BACKGROUND

"DM is associated with an increased risk of CV events. ASA use reduces the risk….but increases the risk of bleeding; the balance of benefits and hazards for the prevention of 1st CV events in patients with DM is unclear."

NEJM 2018;379:1529-1539

DM: ASA for 1^0 Prevention The ASCEND Trial

- DBRPCT Adult DM (n=15,480)
- Rx ASA 100 mg/d vs placebo X 7.4 yrs
- Inclusion:
  - Age >40 (mean = 63)
  - No known CVD
- Outcomes: CV events, major bleeding

ASCEND Study Collaborative Group NEJM 2018;379:1529-1539

DM: ASA for 1^0 Prevention The ASCEND Trial

	ASA	PBO	RR	p
CV Events	8.5%	9.6%	0.88	0.01
Major Bleed	4.1%	3.2%	1.29	0.003
GI CA	2.0%	2.0%	1	NS
All CA	11.6%	11.5%	1	NS

ASCEND Study Collaborative Group NEJM 2018;379:1529-1539

DM: ASA for 1^0 Prevention
The ASCEND Trial

CONCLUSIONS

"ASA use prevented serious vascular events….but it also caused major bleeding…The absolute benefits were largely counterbalanced by the bleeding hazard."

ASCEND Study Collaborative Group NEJM 2018;379:1529-1539

Iatrogenic Hypertension

A 62 y.o. man with long-standing osteoarthritis of the knee has recently noted an increase in BP measured at his local gym
For most of his adult life, BP has been 120-140/76-80 mm Hg.
In the last 3 months, his BP has increased to 150-160/88-94.
Which of the following meds is LEAST likely to have caused an elevation in BP

a) Duloxetine (eg, Cymbalta)
b) Naproxen (eg, Naprosyn, Alleve)
c) Celecoxib (eg, Celebrex)
d) Ibuprofen (eg, Motrin, Advil)

Differential BP Effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM Trial

Frank Ruschitzka, Jeffrey S Borer, Henry Krum, Andreas J Flammer, Neville D Yeomans, Peter Libby, Thomas F Luscher, Daniel H Solomon, M Elaine Husni, David Y Graham, Deborah A Davey, Lisa M Wisniewski, Veun Menon, Rana Fayyad, Bruce Beckerman, Dinu Iorga, A Michael Lincoff, and Steven E Nissen on behalf of the PRECISION-ABPM Investigators

European Heart Journal 2017;38:3282-3292

NSAIDs & BP:
The PRECISION-ABPM Trial

Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement Trial

Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

NSAIDs & BP: Background

- >70 million Rx/year for NSAIDs in USA
  - + OTC → 30 Billion doses/yr
- 2015: FDA labeling warns about CV risk
  - All NSAIDs included
  - COX-2 selective agents included

Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

NSAIDs & BP:
Example At-Risk Populations

- 19% of USA population are 'regular users'
- 30 million USA osteoarthritis patients
  - 40% with comorbid HTN

Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

NSAIDs & BP: PRECISION-ABPM

- STUDY: DBRCT RA/OA patients (n = 444)
- Inclusion
  - Age > 55 years
  - OA (92%)
  - RA (8%)
  - ↑CVD Risk

Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

PRECISION-ABPM "↑ CVD Risk" Criteria

Must have 3 or more of	
Age > 55 (♂) 65 (♀)	Proteinuria
HTN	ABI ≤ 0.9
Dyslipidemia	Waist Hip Ratio ≥.0.9
Fam Hx CVD	LVH
Smoking	Carotid Stenosis ≥50%
Revascularization	CVD event

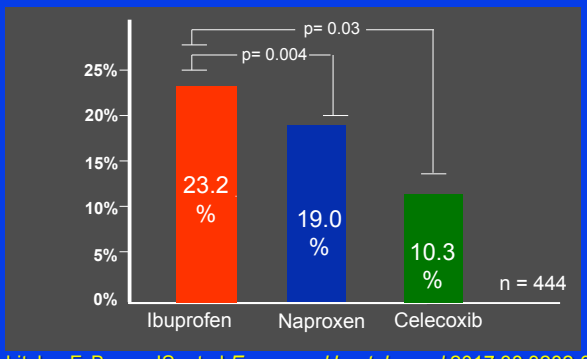
Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

PRECISION-ABPM Rx

- Rx (all X 4 months)
  - Celecoxib 100-200 mg b.i.d.
  - Ibuprofen 600-800 t.i.d.
  - Naproxen 375-500 mg b.i.d.
- Outcome: Normotensive patients who develop HTN (≥130/80 mean BP on ABPM)

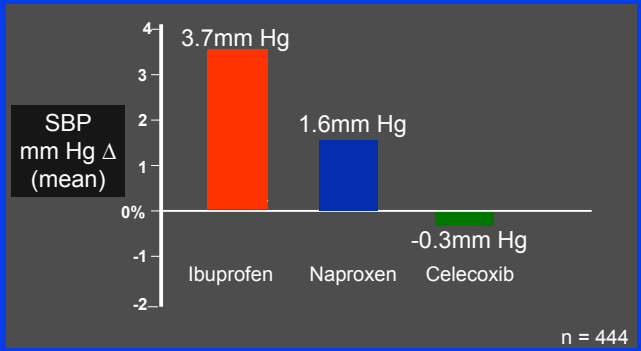
Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

PRECISION-ABPM: Incident HTN



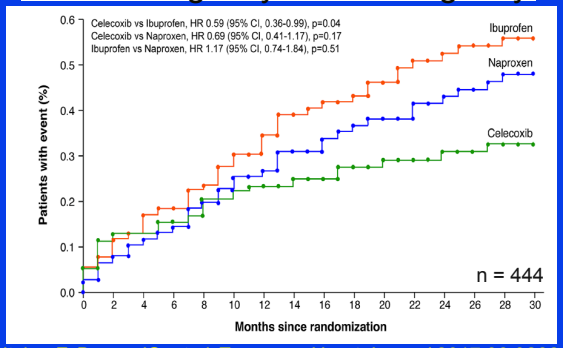
Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

PRECISION-ABPM: Mean SBPΔ



Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

Time To 1st Hospitalization for HTN Emergency or HTN Urgency



Ruschitzka F, Borer JS, et al *European Heart Journal* 2017;38:3282-3292

Duloxetine & BP Δ

- Mean Cross-trial BP Δ: +0.5/0.8 mmHg
- No difference from placebo in sustained HTN (3 consecutive visits)
- Supratherapeutic doses (200 mg b.i.d.)
  - Pulse: ↑ 5-8 bpm
  - BP: ↑ 4.7-6.8/4.5-7.0 mm Hg

Cymbalta Prescribing Information

Safe Use of Metformin

A 66 y.o. man with T2DM has done a good job keeping his A1c <7% with diet and exercise, but the last two 6-monthsly visits the A1c was 7.3 and 7.4. You were thinking of starting metformin, but notice that his eGFR is only 40 (CKD3b). You should

a) Avoid metformin

b) Consider reduced dose metformin (≤1g/d)

c) Use traditional doses of metformin (1g-2g/d)

d) Use a combination metformin/DPP4 agent

Metformin Treatment in Patients with Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4

Jean-Daniel Lalau, Farshad Kajbaf, Youssef Bennis, Anne-Sophie Hurtel-Lemaire, Frans Belpaire, and Marc E De Broe

Diabetes Care 2018;41:547-553

Normal Adult Kidney Function (up to age 40)

	GFR
Normal ♂	100-130 mL/min
Normal ♀	90-120 mL/min
Normal Progression After age 40	-0.4 to -1.2 mL/min/yr

Renal Function *Wikipedia* accessed 018-Oct-9

CKD Stages

Stage	Descriptor	GFR mL/min
1*		>90
2*	Mild	60-90
3a	Moderate	45-59
3b	Moderate	30-44
4	Severe	15-29
5	ESRD	<15

*denotes kidney disease if associated with signs of kidney damage, eg proteinuria

Renal Function *Wikipedia* accessed 018-Oct-9

Metformin Basics

"… metformin is not metabolized, does not bind to proteins, and is rapidly eliminated by the kidneys."

Lalau JD et al Diabetes Care 2018;41:547-553

Metformin Basics

"Consequently most guidelines…discourage the use of metformin in patients with moderate-to-severe CKD because of the fear of lactic acidosis attributed to metformin accumulation."

Lalau JD et al Diabetes Care 2018;41:547-553

Metformin Basics: HOWEVER

"…the strength of the link between metformin and lactic acidosis has been greatly overstated."

Lalau JD et al Diabetes Care 2018;41:547-553

Metformin Progress

"In 2016…the US FDA removed the contraindication on the use of metformin in CKD stages 3A and 3B….However, these decisions were made in the absence of prospective studies."

Lalau JD et al Diabetes Care 2018;41:547-553

Prospective Study of Metformin in CKD Foundation

- Plasma metformin concentrations
  - <2.5 mg/L: WNL
  - 2.5 – 5 mg/L: moderately elevated
  - > 5 mg/L: clearly elevated
- Maximum safe value (FDA): 5 mg/L

Lalau JD et al Diabetes Care 2018;41:547-553

Suggested Metformin Dosing: CKD
(As Per Prospective Dose Ranging Study)

CKD Stage	Suggested Metformin Dose
3A	1.5 g/d (0.5 g qam, 1 g qpm)
3B	1.0g/d (0.5 g qam, 0.5 g qpm)
4	0.5 g/d

Lalau JD et al Diabetes Care 2018;41:547-553

Pesky but 'Innocent' Hemorrhoidal Bleeding

A 45 y.o. male has recurrent rectal bleeding. Recent colonoscopy found only internal hemorrhoids. While bleeding has not been profuse, multiple recurrent episodes in the past have produced modest transient declines in hemoglobin. The patient does not want surgical intervention or banding. You could

a) Apply topical aluminum chloride

b) Treat with fresh frozen plasma

c) Treat with oral tranexamic acid

d) Treat with oral vitamin K

Double-blind, placebo-controlled trial of Tranexamic acid on recent internal haemorrhoid bleeding

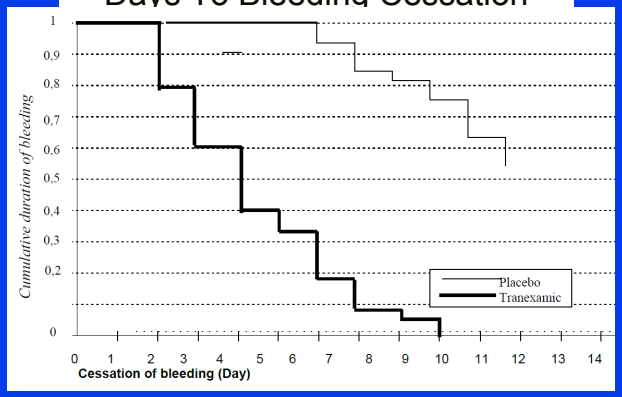
A Aziz Rani *Med J Indones* 2002;11:215-221

Hemorrhoidal Bleeding: Tranexamic Acid

- Study: DBPCT Adults with BRB per-rectum
- Inclusion (n=54):
  - Colonoscopy WNL
  - Hemostatic tests & platelets WNL
  - Actively bleeding
  - Bleeding source: internal hemorrhoids
- Rx: tranexamic acid 500 mg t.i.d. vs placebo X 10 days
- Follow-up: 6 weeks

Rani AA Med J Indonesia 2002;11:215-221

Days To Bleeding Cessation



Rani AA Med J Indonesia 2002;11:215-221

Hemorrhoidal Bleeding Tranexamic Acid Conclusion

"In conclusion tranexamic acid is highly effective to stop recent haemorrhoidal bleeding and prevent further recurrent bleeding."

- Rebleed RR placebo vs tranexamic acid=14.2

Rani AA Med J Indonesia 2002;11:215-221

The Goldilocks Choice

Grandma is an 85 y.o. women with dementia being placed in a nursing home by her daughter. There are 3 available 16' X 16' rooms. Room A is furnished with a 'standard' bed (35"), Room B with an 'intermediate standard' bed (39"), and Room C with a 'large standard' bed (42"). If all three rooms are similarly priced, she should choose

a) Room A: smaller beds allow more movement space

b) Room B: it is the same size she has at home

c) Room C: She is less likely to fall out of bed

d) Goldilocks/schmoldilocks: It makes no difference

PRACTICAL RESEARCH

Examining Bed Width as a Contributor to Risk of Falls from Bed in Long-Term Care

Guy Fragala PhD, Bonnie Perry MS, Maren Fragala PhD

Annals of Long-Term Care: Clinical Care and Aging 2012;20(6):35-38

Bed Size & Falls in Long Term Care: Foundations

- 45%-70% LTC residents fall annually
  - 50% experience multiple falls
  - 50% of falls are from bed
- Previously recognized bed 'risk factors'
  - Softer mattress
  - Elevated mattress height
  - Change in size from home

Fragala G et al *Ann Long-Term Care* 2012;20(6):35-38

LTC Bed Size: Why So Small?

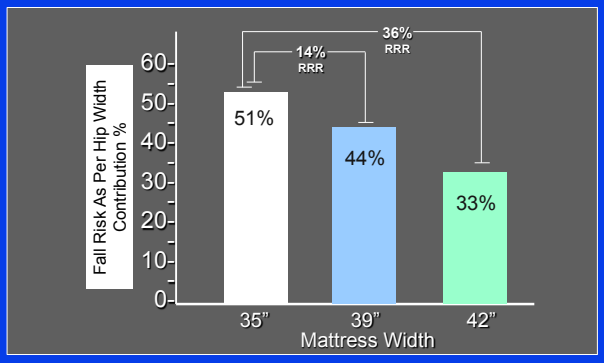
"Traditionally…LTC facilities have surfaces that are 35 inches wide. This seems to have originated from the need to use beds as a transport device, which requires that they fit through a standard 36-inch wide doorway."

Fragala G et al *Ann Long-Term Care* 2012;20(6):35-38

Standard Bed Dimensions: USA

Bed Designation	Width
Twin	39"
Full	54"
Queen	60"
King	76"

Relative Risk of Falls As Per Mattress Width



Fragala G et al *Ann Long-Term Care* 2012;20(6):35-38

LTC Bed Size: Discussion

"Although an acceptable level of risk has not yet been defined, a patient's risk of falling….can be reduced by 36% simply by replacing a 35-inch wide mattress with those that have a width of 42 inches."

Fragala G et al *Ann Long-Term Care* 2012;20(6):35-38

Second-Hand Smoke Exposure

Jay is a 60 y.o. Asian American man who has never smoked. His father smoked heavily at home throughout his upbringing. Compared to non-exposed persons, one could characterize his risk of adverse CV consequences based on this exposure

a) There is no increased risk

b) CHD mortality risk is increased more than 10%

c) Ischemic stroke risk is increased almost 3 X

d) All cause mortality is statistically increased, but of marginal clinical significance

CHEST Original Research

COPD

Secondhand Smoke Exposure Predicted COPD and Other Tobacco-Related Mortality in a 17-Year Cohort Study in China

Yao He, MD, PhD; Bin Jiang, MD, PhD; Liang Shou Li, MD; Lan Sun Li, MD; Lisanne Ko, PhD; Lei Wu, MB; Dong Ling Sun, MD, PhD; Shu Fang He, MD; Bao Qing Liang, MD; Frank B. Hu, MD, PhD; and Tai Hing Lam, MD

He Y et al CHEST 2012;142(4):909-918

2nd Hand Smoke Toxicity

- Study: 18 year f/u Chinese never-smoking ♂ and ♀(n =910)
- 2nd Hand Exposure:
  - Home: 44.2%
  - Work: 52.9%
  - Both: 67.1%
- Outcomes: CHD, lung CA, all-cause mortality

He Y et al *CHEST* 2012;142(4):909-918

2nd Hand Smoke Toxicity Results

Outcome	RR (CI)
CHD Mortality	2.15 (1.00-4.61)
Ischemic Stroke	2.88 (1.10-7.55)*
Lung CA	2.00 (0.62-6.40)
COPD	2.30 (1.06-5.00)*
All cause mortality	1.72 (1.29-2.20)*

*p < 0.05

He Y et al *CHEST* 2012;142(4):909-918

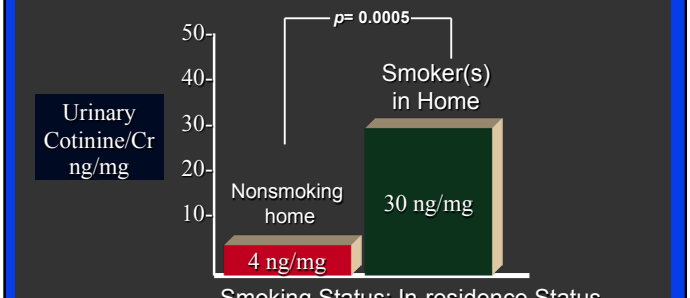
2nd Hand Smoke Toxicity Conclusions

"This study shows dose-response relationships between SHS and major tobacco-related mortality and provides new evidence to support causation for COPD and ischemic stroke."

*p < 0.05

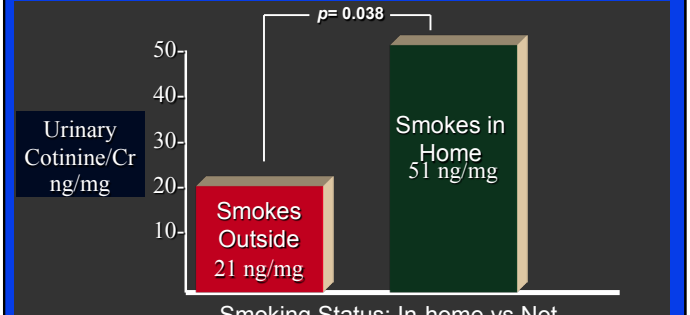
He Y et al *CHEST* 2012;142(4):909-918

Urinary Cotinine in Children Effect of at-home Smokers



Winkelstein ML, Tarzian A, Wood RA "Parental Smoking Behavior and Passive Smoke Exposure in Children with Asthma" Ann Allergy Asthma Immunol 1997;78(4):419-423

Don't Worry, Doc, We Only Smoke Outside!



Winkelstein ML, Tarzian A, Wood RA "Parental Smoking Behavior and Passive Smoke Exposure in Children with Asthma" Ann Allergy Asthma Immunol 1997;78(4):419-423

Consequences to Children of Environmental Tobacco Smoke

"Exposure to environmental tobacco smoke increases children's risk for developing middle ear infections, bronchitis and pneumonia, coughing and wheezing, compromised lung function and asthma….children with asthma whose parents smoke have more severe Sx and more frequent exacerbations."

Kuehn BM "Tobacco Smoke Exposure Among Children" JAMA 2013;310(12):1218-1219

Xerostomia In a Nursing Home Resident

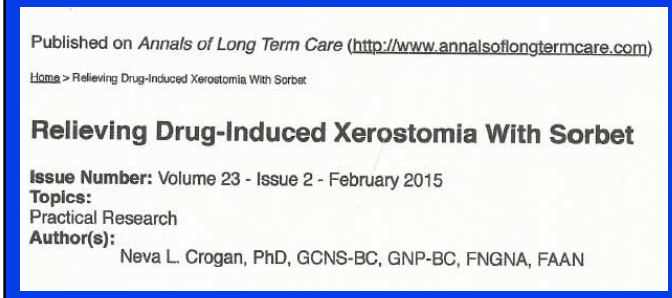
Martha is an 82 y.o. woman taking solifenacin (Vesicare) for OAB. Since her admission to a nursing home 6 months ago, she has lost almost 20#. She manifests no signs of illness, but is conspicuously eating less food, and complains of dry mouth. Which intervention might help her

a) Switch to darifenacin (Enablex)

b) Switch to oxybutynin (Ditropan)

c) Add a pro-cholinergic like donepezil (Aricept)

d) Provide pre-meal sorbet



Published on *Annals of Long Term Care* (http://www.annalsoflongtermcare.com)

Home > Relieving Drug-Induced Xerostomia With Sorbet

Relieving Drug-Induced Xerostomia With Sorbet

Issue Number: Volume 23 - Issue 2 - February 2015
Topics:
Practical Research
Author(s):
Neva L. Crogan, PhD, GCNS-BC, GNP-BC, FNGNA, FAAN

Undernutrition: Scope of the Problem

- Inadequate food intake: ≤85% NH elders
- Consequences:
  - Weight loss
  - Undernutrition
  - ↓ QOL
  - Functional decline
  - Morbidity, mortality

Crogan NL *Ann Long Term Care* 2015;23(2):17-21

Undernutrition: Common Causes

- Anorexia
- Chronic disease
- Sensory loss
- Oral problems
- Dental problems
- Iatrogenic
- Unpalatable food

Adapted from Crogan NL *Ann Long Term Care* 2015;23(2):17-21

Xerostomia: What's the Big Deal?

"Many older adults living in nursing homes suffer from inadequate food intake 2^0 to xerostomia…. [and] have difficulty forming a food bolus, swallowing, and tasting food, all of which contribute to diminished nutritional intake."

Crogan NL *Ann Long Term Care* 2015;23(2):17-21

Xerostomia: Common Iatrogenic Causes

- Anticholinergics
- Antihistamines
- Sympathomimetics
- Radiation
- Chemotherapy

Crogan NL *Ann Long Term Care* 2015;23(2):17-21

Sorbet for Drug-Induced Xerostomia

- Study: Cognitively intact NH residents (n=39)
- Inclusion
  - Xerostomia complaint
  - ≥2 Meds associated with xerostomia
  - Age ≥65 years
  - Meals eaten in NH dining room
  - Meals completed within 1 hour

Crogan NL *Ann Long Term Care* 2015;23(2):17-21

Sorbet for Drug-Induced Xerostomia

- Method: Pre-Rx/Post-Rx design
- Rx: 2 ounces sugar-free lemon-lime sorbet pre-lunch and pre-dinner x 6 weeks
- Outcomes:
  - Fluid intake
  - Food intake
  - Weight

Crogan NL *Ann Long Term Care* 2015;23(2):17-21

Sorbet for Drug-Induced Xerostomia Results at 6 weeks (22 completers)

Mealtime Intake	preRx	On-Rx	P value
Liquids	356 ml	310 ml*	0.002
Food	208g	253g*	0.001

*p <0.05

Weight	Gained	No Δ	Lost
	36%	45%	18%

Crogan NL *Ann Long Term Care* 2015;23(2):17-21

Sorbet for Drug-Induced Xerostomia Conclusion

"…offering 2 ounces of sorbet prior to meals can help ameliorate drug-induced xerostomia and improve food intake among elderly nursing home residents."

Crogan NL *Ann Long Term Care* 2015;23(2):17-21

SELF EVALUATION

Things I Wish I Knew Last Year

1. Your newly 52 y.o. T2DM is otherwise healthy and in good control on metformin 1 g b.i.d. Should he take ASA for 10 prevention?

a. Yes. DM is a 'CV risk equivalent', thus all Rx is considered 2^0 prevention and of substantial value
b. Yes. Benefits > Risks for 1^0 prevention hypoglycemia outweigh benefits
c. No. Risks > Benefits for 1^0 prevention
d. Maybe: Risks ±= Benefits

2. A 62 y.o. man with long-standing osteoarthritis of the knee has recently noted an increase in BP measured at his local gym. For most of his adult life, BP has been 120-140/76-80 mm Hg. In the last 3 months, his BP has increased to 150-160/88-94. Which of the following meds is LEAST likely to have caused an elevation in BP

a. Duloxetine (eg, Cymbalta)
b. Naproxen (eg, Naprosyn, Alleve)
c. Celecoxib (eg, Celebrex)
d. Ibuprofen (eg, Motrin, Advil)

3. A 66 y.o. man with T2DM has done a good job keeping his A1c <7% with diet and exercise, but the last two 6-monthly visits the A1c was 7.3 and 7.4. You were thinking of starting metformin, but notice that his eGFR is only 40 (CKD3b). You should

a. Avoid metformin
b. Consider reduced dose metformin (≤1g/d)
c. Use traditional doses of metformin (1g-2g/d)
d. Use a combination metformin/DPP4 agent

4. A 45 y.o. male has recurrent rectal bleeding. Recent colonoscopy found only internal hemorrhoids. While bleeding has not been profuse, multiple recurrent episodes in the past have produced modest transient declines in hemoglobin. The patient does not want surgical intervention or banding. You could

a. Apply topical aluminum chloride
b. Treat with fresh frozen plasma
c. Treat with oral tranexamic acid
d. Treat with oral vitamin K

5. Grandma is an 85 y.o. women with dementia being placed in a nursing home by her daughter. There are 3 available 16' X 16' rooms. Room A is furnished with a 'standard' bed (35"), Room B with an 'intermediate standard' bed (39"), and Room C with a 'large standard' bed (42"). If all three rooms are similarly priced, she should choose

a. Room A: smaller beds allow more movement space
b. Room B: it is the same size she has at home
c. Room C: She is less likely to fall out of bed
d. Goldilocks/schmoldilocks: It makes no difference

6. Jay is a 60 y.o. Asian American man who has never smoked. His father smoked heavily at home throughout his upbringing. Compared to non-exposed persons, one could characterize his risk of adverse CV consequences based on this exposure

a. There is no increased risk
b. CHD mortality risk is increased more than 10%
c. Ischemic stroke risk is increased almost 3 X
d. All cause mortality is statistically increased, but of marginal clinical significance

7. Martha is an 82 y.o. woman taking solifenacin (Vesicare) for OAB. Since her admission to a nursing home 6 months ago, she has lost almost 20#. She manifests no signs of illness, but is conspicuously eating less food, and complains of dry mouth. Which intervention might help her

a. Switch to darifenacin (Enablex)
b. Switch to oxybutynin (Ditropan)
c. Add a pro-cholinergic like donepezil (Aricept)
d. Provide pre-meal sorbet

Answer Key: 1. D, 2. A, 3. B, 4. C, 5. C, 6. C, 7. D

Commander John J. Burke

John J. Burke, of Cincinnati, Ohio, retired as the Commander of the Greater Warren County, Ohio, Drug Task Force and of the Southern Ohio High Intensity Drug Trafficking Area (HIDTA) in 2015, an operation which included focus on pharmaceutical diversion. He is president of Pharmaceutical Diversion Education, Inc. (PDE), a company providing education and training to health professionals, law enforcement, and regulatory agents on the issues of prescription drug abuse, and the balance required between pain management and drug diversion.

Commander Burke has been a law enforcement officer for 49 years and in 1990 was asked to establish the Cincinnati Police Department's Pharmaceutical Diversion Squad, one of the first units of its kind in the United States, where he pioneered the development of policies and procedures unique to the investigation of prescription drug abuse. He lectures nationally, has authored a monthly column on drug diversion in *Pharmacy Times* magazine for the past 15 years, and is the past president of the National Association of Drug Diversion Investigators. In 2015 he co-founded the International Health Facility Diversion Association and is the current President of this non-profit organization which provides training and networking for healthcare facility diversion professionals with the link available at www.ihfda.org

You may contact Commander Burke at (513) 623-3278 or, by email at Burke@rxidversion.com.

Commander John J. Burke
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Prescription Drug Abuse: The Scope of the Problem

PHARMACEUTICAL DIVERSION EDUCATION INC.

- John Burke, President & Owner
- www.rxdiversion.com
- Provide prescription drug education to health professionals, law enforcement, & the general public
- Provide expert witness testimony
- Coordinate and present conferences on abuse and diversion of Rx drugs in health facilities

PHARMACEUTICAL DIVERSION

- DEFINITION?
- "Any criminal act involving a prescription drug"

USE OF PAIN MEDICATIONS

- Approximately 10% of the U.S. population is prescribed CS pain in relievers in any one quarter
- A percentage of those medications are diverted for illegal use
- Source: RADARS® systems 2013

PHARMACEUTICAL DIVERSION

- Best Rx drugs for pain have historically been the best drugs to obtain a "high"
- Successful pain drugs=increased prescribing=more of the Rx drugs available=more abuse of those drugs
- Increases demand and street values
- Compromise of extended release Rx drugs=euphoria!

RX UNINTENTIONAL OVERDOSE DEATHS

- Average of 11 people die every day in Ohio and Florida
- Ohio's Rx OD deaths now exceeds those contributed by motor vehicle crashes
- Rx abuse and diversion is nothing new
- Prominent in all communities in the U.S.
- Continued apathy by some law enforcement agencies

SOURCE OF DIVERTED RX DRUGS

- Forged and altered prescriptions
- "Doctor shoppers"
- Prescribers & dispensers of Rx drugs
- Theft (Health facility & Other)
- Package theft/diversion (UPS, DHL, Fed Ex)
- Internet
- Pharmacy robbery and burglary

PHARMACY ROBBERIES

- Usually addicted perpetrator involved
- CII's often the target
- Weapon or threat of weapon involved
- Potentially very dangerous situation
- Rx Patrol should be utilized
- www.rxpatrol.com

INTERNET PHARMACIES

- National Association of Boards of Pharmacy (NABP) check on Internet pharmacies
- NABP indicates that 7,234 Internet drug websites are NOT recommended
- 6,018 (83%) do not require a valid script, consultation with an Rph or take insurance
- Only 3.4% of those reviewed appeared to be "potentially legitimate"

SAFEGUARDING RX MEDICATION

- #1 drug of abuse of 12-17 year olds is Rx drugs
- Top source of those drugs are from your PT's medicine cabinets
- PT's need to realize that they can be the source of Rx drugs for teens and others
- Locking up their medications is essential
- Go to www.guardyourmeds.org

SAFEGUARDING RX MEDICATION

- PT's need to survey their Rx medication stock on hand
- Properly discard those medications that are outdated or are no longer being used
- Requires crushing drugs into undesirable products- diapers, coffee grinds, etc.
- Locate drop box in local LE agency
- www.rxdrugdropbox.org for locations in U.S.

TOP RX DRUGS OF ABUSE

- **Hydrocodone (Vicodin, Lortab, Norco)**
- #1 prescribed Rx drug in the U.S.
- #1 abused Rx drug in the U.S.
- October 2014 became a CII drug
- Drug is typically abused intact orally
- Street values approximately $1 per milligram
- 15-20 pills per day typical addiction level
- Not impossible to go much higher

TOP RX DRUGS OF ABUSE

- **Oxycodone (Percocet, Roxicodone)**
- CII drug
- Oxycodone Immediate Release (IR) 30 mg. very popular currently
- Injected, snorted, chewed and swallowed
- Street values typically $1 per milligram
- Favorite drug of pill mills

TOP RX DRUGS OF ABUSE

- **Alprazolam (Xanax)**
- #1 benzodiazepine of abuse
- More popular due to quick release into the body
- 20-30 per day habit very possible
- Typical street values $3 per pill
- Rounds out top 3 Rx drugs of abuse for LE (Hydrocodone, oxycodone, alprazolam)

TOP RX DRUGS OF ABUSE

- Methadone ($10-$40 per dose)
- Stimulants (Ritalin/Adderall)
- Buprenorphine (Subutex/Suboxone)
- Tramadol (Ultram)
- Diazepam (Valium)
- Fentanyl (Duragesic/Actiq)

"Abuse Deterrent Formulations-Do They Work?" A Law Enforcement Perspective

Abuse Deterrent Formulations (ADF)

- FDA has declared several CII Extended Release Opioid Rx drugs to be Abuse Deterrent Formulations (ADF)
- OxyContin® was the first ADF designated by the FDA in the spring of 2010
- OxyContin® was examined due to the extensive abuse and considerable data not available with the other ADF drugs

OxyContin® Abuse

- First signs of abuse in the late 1990's
- Initial reports of abuse and diversion discovered in Maine
- Abuse & Diversion quickly spread for over a decade
- Pills were easily crushed and then snorted, chewed, injected, or free-based
- Street values easily reach $1 mg.
- LE inundated with OxyContin® abuse issues

OxyContin® Reformulation

- August 2010 reformulated pills on retail market from Purdue Pharma
- New version designed to be difficult to compromise
- Indicia change from "OC" to "OP"
- Pill color and size virtually identical
- Excellent opportunity to determine success or failure of reformulation

North Carolina House Select Committee March 23, 2016 Testimony

SBI INPUT

Judy Billings, special agent in charge of the SBI's Diversion and Environmental Crimes Unit, said one of the most compelling examples of the significance of opioids with abuse-deterrent properties is the reformulation of OxyContin and its effect.

"As an investigator with the SBI in our Diversion and Environmental Crimes Unit, I personally have seen a dramatic decrease in the diversion, misuse and abuse of OxyContin after the reformulation of the medication, especially once the generic form that had no tamper resistant measure was taken off the market," Billings said in a letter to the committee. "Since 2010 our agency has seen a remarkable decrease in the diversion and seizure of OxyContin products involving street sales."

There were no seizures by the SBI in 2014, 2015 or to date in 2016, she said.

"When involved in undercover purchases of pharmaceutical controlled substances, you cannot give OxyContin away," Billings said. "Abusers and addicts do not want it due to the reformulation and their inability to design a measure to defeat the tamper resistant mechanism."

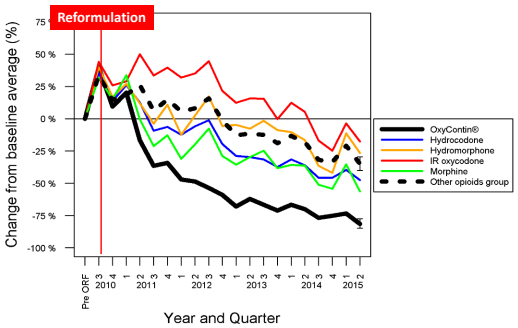
RADARS® Drug Diversion Survey

- OxyContin® ER Investigations Decreased by over 75% After Reformulation
- Reports from Drug Diversion Survey of 250 Agencies Reporting in 49 States
- Similar Results Seen in Other RADARS® Survey Reports
- Dr. Steven Kurtz- Nova SE University, Miami, Florida

RADARS Drug Diversion Program

Drugs Involved in Investigations, past 90 days, 2009 – 2015 (Figure 2)

- 250 law enforcement investigators in 49 states



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Rx Patrol®

- Developed and funded by Purdue Pharma
- Tracks pharmacy robberies nationwide
- Reports indicate weapon, description, and drugs demanded by robber
- Reports track time of day, day of the week most likely for pharmacy robbery
- Provides LE ability to solve robberies occurring in multiple jurisdictions nationwide

Rx Patrol % of Robberies involving OxyContin®

- 2009 - 73.15%
- 2010 - 64.24% (ADF Introduced 8/10)
- 2011 - 26.68%
- 2012 - 22.44%
- 2013 - 22.15%
- 2014 - 12.29%
- 2015 - 10.7%
- 2016 - 8.1%
- 2017- 7.4%

Rx Patrol®

- Why is this significant?
- Armed robbers can demand any drug on the shelf and they are free!
- Demand for OxyContin® drops over 65% after the reformulation
- Addicts drug choice mirrors the street demand and reflects street values both of which have dropped dramatically

OxyContin® Abuse 2019

- Reformulated OxyContin® can be abused
- Must swallow multiple pills intact to achieve "high"
- Hardened addicts most likely to OD and die will not use intact
- They need the jolt of injection or snorting
- Difficult and time consuming to accomplish this with the ADF OxyContin®

Heroin & ADF's

- Mexican Cartels definitely ramped up heroin production just months before OxyContin® reformulation hit the streets
- If the ADF was successful, the Cartel knew that thousands of addicts would need a "fix"
- They merely provided a similar and cheaper product
- Addition of fentanyl and now carfentinil are large percentage of opioid related deaths

Future of ADF's

- ADF effectiveness on OxyContin® is clear
- Abuse of other ADF opioids seem to mirror OxyContin®
- ADF's makeup vary from company to company
- ALL ADF's have the ability to be compromised
- The difficulty and time consumption required may dictate whether the compromise is effective enough

ADF's & Pain Patients

- If ADF's continue to be effective, they will be a huge positive for legitimate pain patients
- Physicians will feel more comfortable in prescribing ADF's knowing that abuse probabilities are very low
- Pain patients will be able to consume a drug that provides pain relief while prescribers concerns of abuse should be limited

ER DRUG SEEKERS

- Slam car doors and trunks on hands
- Slam windows on hands and fingers
- Carry syringes with blood to squirt in their mouth to obtain Demerol
- Carry kidney stones in a jar to the ER
- Insert objects into open wounds
- Deliberately irritate root canal work
- Beat on foot with 4.5 pound hammer

PRESCRIPTION MONITORING PROGRAMS (PMP)

- PMP's in 49 states
- Missouri is only state without a PMP
- Enacted by states to track the prescribing/dispensing of Rx drugs
- Most involve only CS
- Varied availability access for LE
- Valuable tool for investigators if accessible

PRESCRIPTION MONITORING PROGRAMS (PMP)

- Valuable tool for prescribers and dispensers of CS
- Electronic databases
- Can identify diversion and reduce healthcare fraud
- Must include LE and HP access for maximum effectiveness
- Inter Connect- NABP program

ILLEGAL PRESCRIBER INVESTIGATIONS

- Rx drugs for sex
- Rx drugs for money
- Rx drugs for illicit drugs
- Healthcare fraud
- Personal or family member impairment
- Senile practitioner

PAST CASES

- Prescriber recorded bra and panty colors and sizes of all female patients
- Prescriber threatened females removal from worker's compensation program unless they engaged in sex
- Prescriber financed undercover morphine operation

PAST CASES

- Classic Ohio case- prescriber involved in massive prescribing of CS
- Office had no staff, telephone or appointments
- PT's could drink beer and smoke cigarettes in waiting room
- Long lines outside of office commonplace
- Case concluded when prescriber attempted to exchange scripts for automatic weapons!

WHAT'S THE POINT?

- All of the examples the prescribers were significantly outside of the scope of legitimate medical practice
- Per the FSMB- less than 1/10 of 1% of physicians are sanctioned for anything
- Not a crime to be duped!
- Physicians should prescribe based on their training and experience- not fear of LE

WHY GET INVOLVED IN REDUCING DIVERSION?

- Drug seekers keep you from legitimate patients
- Lack of addressing the issue will only increase the problem
- Perpetuates patient's addiction or trafficking by ignoring the problem
- Could increase LE scrutiny

SELF EVALUATION

Prescription Drug Abuse: The Scope of the Problem

1. According to RADARS, what is the approximate percentage of the U.S. population prescribed controlled substances at any one time?

a. 20%
b. 50%
c. 10%
d. 2%

2. What are the top 3 controlled substances of abuse?

a. Oxycodone, alprazolam, hydrocodone
b. Hydrocodone, hydromorphone, diazepam
c. Oxymorphone, hydrocodone, alprazolam
d. Meperidine, oxycodone, morphine

3. T/F - One of the top sources of 12-17 YOA for Rx drugs is your medicine cabinet.

4. T/F - OxyContin experienced a significant spike in diversion after the reformulation was introduced?

5. T/F - The only U.S. state without a prescription monitoring program currently is Alaska.

6. Top methods criminal prescribers utilize to divert medication

a. Rx drugs for sex
b. Rx drugs for money
c. Rx drugs for illicit drugs
d. All of the above

7. T/F - One of the main reasons for prescribers to address diversion in their practice is that it keeps them from time with legitimate patients.

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

C. Wayne Weart, PharmD, FASHP, BCPS

C. Wayne Weart, PharmD, of Charleston, South Carolina, is professor of the Department of Clinical Pharmacy and Outcome Sciences at Medical University of South Carolina (MUSC) College of Pharmacy, as well as professor 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 at (843) 792-3606 or by email at weartcw@musc.edu.

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Pharmacotherapy Update - Parts 1 & 2

HPV9 Vaccine (Gardasil-9) by Merck

- December 10, 2014 The FDA approved nine-valent HPV vaccine (V503, **Gardasil-9) that includes coverage for 6, 11, 16, and 18—just like HPV4—but also for five additional high cancer-risk strains: 31, 33, 45, 52, and 58.**
  - What might it offer vs. the current vaccines?
    - Additional 25% CIN 2 or cervical lesions
    - Additional 18% vaginal cancer cases
    - Additional 15% cervical cancer cases
    - Additional 4% of oropharyngeal cancer cases
    - The **FDA has stated that "Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers."**

ACIP Meeting 10-19-2016

- The **ACIP recommended that 11- to 12-year-olds receive 2 doses of human papillomavirus (HPV) vaccine at least 6 months apart rather than the previously recommended 3 doses** to protect against cancers caused by HPV infections. **Teens and young adults who start the series later, at ages 15 through 26 years, will continue to need 3 doses of HPV vaccine** to protect against cancer-causing HPV infection.
- October 7, 2016, the FDA approved adding a 2-dose schedule for 9-valent HPV vaccine (Gardasil 9) for adolescents aged 9 through 14 years

HPV-9 Vaccine

- **What is the recommendation for persons with immunocompromising conditions?**
- **CDC recommends 3 doses of HPV vaccine (0, 1–2, 6 months) for immunocompromised people age 9 through 26 years.**
- People whose immune responses might be lower, for example due to **HIV infection, cancer, autoimmune disease, or taking immunosuppressant medications, should receive 3 doses to make sure they get the most benefit.**
- However, children with asthma, diabetes, and other conditions that would not suppress immune response to HPV vaccination can receive a 2-dose schedule.

HPV-9 Vaccine

- **October 5, 2018 the FDA approved** Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant **(Gardasil-9) expanding the approved use of the vaccine to include women and men aged 27 through 45 years of age**.
- In approximately **3,200 women 27 through 45 years of age, followed for an average of 3.5 years, HPV-9 vaccine (Gardisil-9) was 88 percent effective in the prevention of a combined endpoint of persistent infection, genital warts, vulvar and vaginal precancerous lesions, cervical precancerous lesions, and cervical cancer related to HPV types covered by the vaccine.**
- **Data in men is based upon immunogenicity data from a clinical trial in which 150 men, 27 through 45 years of age, received a 3-dose regimen of HPV-9 vaccine (Gardasil-9) over 6 months.**
- **The ACIP reviewed the data on October 25, 2018 and may take a vote during one of the 2019 meetings?**

Tdap (Adacel Vaccine) by Sanofi Pasteur

- **January 15, 2019 - The Food and Drug Administration (FDA) has expanded the use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis [Tdap] vaccine adsorbed (Adacel, Sanofi Pasteur) to allow for repeat vaccination in patients 10–64 years old ≥8 years after the first Tdap vaccination.** Adacel is approved for active booster immunization against tetanus, diphtheria, and pertussis.
- The approval was **based on data from the Td537 study** which included individuals 18–64 years old who had received a dose of Adacel 8–12 years prior (N=1330). **Participants were randomized to receive either a second dose of Adacel (N=1002) or Td vaccine (tetanus and diphtheria toxoids adsorbed; N=328).** Blood samples for immunogenicity analyses were obtained from participants pre-vaccination and approximately 28 days post-vaccination, the **rates of seroprotection against tetanus and diphtheria were >99% in both groups**.

Hepatitis A Update 2018

- **ACIP Meeting Oct 2018: Hepatitis A vaccination: Homelessness**
  - ACIP Working Group Recommendations:
    - **Pros:** Protection of a vulnerable population
    - Providers are more likely to administer vaccine to homeless persons if homelessness is an ACIP recommended indication for vaccination
    - Vaccination of homeless persons would reduce an at risk population and therefore reduce the risk of large-scale outbreak, and increase the herd immunity among the homeless population over time
    - Vaccinating homeless in an outbreak setting and controlling an outbreak among homeless is challenging compared to integrating services into a familiar setting
    - Routine vaccination is likely less costly than vaccination as part of an outbreak response
    - **Cons:** Vaccine administration record-keeping
    - Limited published data exist on hepatitis A or vaccination that specifically focuses on persons who are homeless
    - Routine vaccination of homeless who do not utilize health services might not be feasible

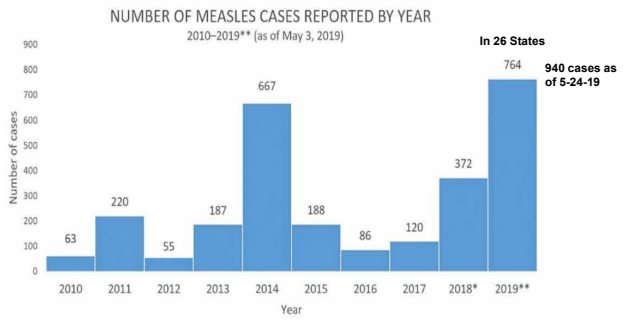
FDA Head Warns Feds May Intervene if States Don't Strengthen Vaccine Laws

- 2-20-2019 FDA commissioner Scott Gottlieb said that the **federal government may have to take action if states don't strengthen their laws on vaccine exemptions**, CNN reports.
- **Seventeen states allow families to choose not to vaccinate their children based on personal beliefs. Forty-seven states allow religious exemptions.**
- **Measles outbreaks in the U.S. have infected 127 people so far in 2019; most were unvaccinated. (4/3/2019 465 cases including 150+ from Rockland County, NY)**

'Unethical Physicians' Aid Surge in Vax Exemptions

- At **two public charter schools in the Sonoma wine country town of Sebastopol, more than half of the kindergartners received medical exemptions from state-required vaccines last school year.** The **cities of Berkeley, Santa Cruz, Nevada City, Arcata, and Sausalito all had schools in which more than 30% of the kindergartners had been granted such medical exemptions. (CDC estimates medical exemptions should be a fraction of 1% and include children who are allergic to vaccine components, who have had a previous reaction to a vaccine, or whose immune systems are compromised, including kids being treated for cancer).**
- Nearly **three years ago**, with infectious disease rates ticking up, **California enacted a fiercely contested law barring parents from citing personal or religious beliefs to avoid vaccinating their children. Children could be exempted only on medical grounds, if the shots were harmful to health. (Miss, WV and now Maine have passed similar legislation while Washington has just eliminated the personal exemption)**
- **Some physicians are wielding that power liberally and sometimes for cash: signing dozens -- even hundreds -- of exemptions for children in far-off communities.** (MedPage Today 4-10-2019)

US Measles Cases and Outbreaks



https://www.cdc.gov/measles/cases-outbreaks.html

Measles

- Acute viral illness with prodrome of fever, malaise, cough, coryza (runny nose), and conjunctivitis, followed by maculopapular rash
- Potential complications: pneumonia, encephalitis, and death
- Measles is highly infectious Average incubation period (between exposure and rash onset): 14 days (range, 7-21 days)
- **Before the U.S. measles vaccination program started in 1963, each year in the U.S.**
  - **3–4 million people got measles**
  - **400–500 of them died**
  - **48,000 were hospitalized**
  - **4,000 developed encephalitis because of measles**

Measles

- **In 2000, endemic measles was declared "eliminated" from the U.S.** (absence of continuous disease transmission for greater than 12 months)
- **Importation of measles will continue to occur as measles is endemic in many other parts of the world.**
- Measles cases are still reported in the U.S., including among adults - **Most cases related to travelers who bring measles back from overseas (2/3 from unvaccinated U.S. residents, 1/3 from unvaccinated foreign visitors)**
- **2 doses of MMR (measles-mumps-rubella) vaccine are 97% effective at preventing measles; 1 dose is 93% effective. Protection lasts for life.**
- The majority of people who get measles are unvaccinated.
  - http://www.immunize.org/cdc/cdc-measles-us-3-28-2019.pdf

Mumps Outbreak

- Update: **Mumps Outbreak at Temple University in Philadelphia March 25, 2019**
- Following a large second wave of transmission, the **number of mumps cases associated with the Temple University outbreak has increased to 99.**
- Recognition, Testing, and Management:
  - When evaluating patients with parotitis without an apparent cause, area providers should recognize the increased likelihood of mumps infection among patients who are associated with Temple University and **consider mumps infection in other patients with parotitis.**

Mumps Outbreak

- When mumps is suspected, providers should:
  - **Place patients with suspected mumps on droplet precautions**, which includes the use of surgical masks for healthcare workers with close patient contact.
  - Collect a buccal swab, urine, and serum for mumps testing.
  - **Advise patients** who have suspected or confirmed mumps infections to **self-isolate, avoid travel**, and **limit close contact with others for 5 days following onset of parotitis.**
  - **PDPH recommends a booster dose of MMR vaccine for students who are at at-risk of exposure to the mumps virus. This includes catch-up vaccination for the 2-dose MMR series or a 3rd dose for students who have previously received the routine 2-dose series.**

Baloxavir marboxil (Xofluza) by Shionogi/Roche

- **Oct 24, 2018 the FDA approved baloxavir marboxil (Xofluza) for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.** The drug is the first new medication for influenza with a novel mechanism in the last 20 years and it was **granted Priority Review by the FDA.**
- A **single-dose oral medicine** with a novel proposed mechanism of action that **inhibits polymerase acidic endonuclease, an enzyme essential for viral replication** with **demonstrated efficacy against a wide range of influenza viruses, including oseltamivir-resistant strains and avian strains** (H7N9, H5N1) in non-clinical studies.
- In clinical trials of baloxavir marboxil, **resistant viruses were detected in 23.4 percent of participating patients younger than 12 years old in Japan.**

Baloxavir marboxil (Xofluza)

- **CAPSTONE-1 was a phase III multicenter, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of Xofluza in 1,436 people age 12 and older in the US and Japan during the 2016-2017 season.**
- The primary endpoint of the study was time to alleviation of symptoms.
- Doses: **weight-based single doses of baloxavir (40-79 Kg = 40 mg and ≥ 80 Kg = 80 mg) and oseltamivir 75 mg twice daily for 5 days. (Available as 2 or 4 x 20 mg tabs and 1 or 2 x 40 mg tabs per blister card) ~$165.00/single dose GoodRx.com 11-26-18**
- **Oseltamivir (Tamiflu) 75 mg x 10 caps Brand ~$165.00 and generic ~$50.00 GoodRx.com 11-26-18**
  - N Engl J Med 2018; 379:913-923

Baloxavir marboxil - Xofluza

- The **median time to alleviation of influenza symptoms was 23.4 to 28.2 hours shorter in the baloxavir groups than in the placebo group (P<0.05).** In the phase 3 trial, the intention-to-treat infected population included 1064 patients; **84.8 to 88.1% of patients in each group had influenza A(H3N2) infection. The median time to alleviation of symptoms was 53.7 hours (95% confidence interval [CI], 49.5 to 58.5) with baloxavir, as compared with 80.2 hours (95% CI, 72.6 to 87.1) with placebo (P<0.001).** The **time to alleviation of symptoms was similar with baloxavir and oseltamivir (median time 54 hours versus 54 hours).** Baloxavir was associated with greater reductions in viral load 1 day after initiation of the regimen than placebo or oseltamivir. (N Engl J Med 2018; 379:913-923)
- Adverse events were reported in 20.7% of baloxavir recipients, 24.6% of placebo recipients, and 24.8% of oseltamivir recipients.

Baloxavir marboxil (Xofluza)

- Roche recently announced that the **global phase III CAPSTONE-2** study assessing the safety and efficacy of baloxavir marboxil in people at high risk of complications from the flu, as defined by the CDC, met the study's primary objective and showed superior efficacy in the primary endpoint of time to improvement of influenza symptoms versus placebo.
  - Result: Among **2184 randomized pts**, 1163(53%) comprised the ITTI population **(47.9% A/H3N2, 6.9% A/H1N1, 41.6% B)**. The most common risk factors were **asthma or chronic lung disease(39.2%) and age ≥65 years (27.4%). Time to improvement in flu symptoms (**TTIIS) was **significantly shorter in BXM than PLC (median 73.2hr vs 102.3hr, p<0.0001) and numerically shorter than Os (81.0 hr, p=0.8347).** TTIIS in BXM pts with A/H3N2 virus (median: 75.4 hr) was significantly shorter than in PLC (100.4 hr; P =0.0141) and was significantly shorter in pts with influenza B (74.6 hr) than in either PLC (100.6 hr; P =0.0138) or Os (101.6 hr; P =0.0251). (ID Week 2018 Late Breaker-Saturday, October 6, 2018: 10:50 AM)

Baloxavir marboxil (Xofluza)

- **T1/2 ~ 79 hours**
- Weight based dose taken with or without food
- **Co-administration of baloxavir with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids or oral supplements (e.g., calcium, iron, magnesium, selenium, or zinc) reduce plasma concentrations and should be avoided.**
- LAIV should not be considered effective if treated with baloxavir if administered concurrently or within about 2 weeks after LAIV

Baloxavir marboxil (Xofluza)

- Baloxavir will also be further studied in a phase III development program including pediatric populations, post-exposure prophylaxis and severely ill hospitalized people with influenza, as well as to assess the potential to reduce transmission in otherwise healthy people.
- Oseltamivir: Treatment of acute, uncomplicated influenza A and B in patients 2 weeks of age and 1 year of age who have been symptomatic for no more than 48 hours. (3 mg/Kg BID x 10 days of 6 mg/ml oral susp)
- Treatment/Prophylaxis of influenza A and B in patients 1 year and older is weight based. 15 kg or less 30 mg BID/30 mg QD; 15.1-23 kg 45 mg BID/45 mg QD; 23.1-40 kg 60 mg BID/60 mg QD; >40 kg adult dose

Baloxavir marboxil (Xofluza)

- Researchers in Japan find evidence that some strains (6 to date) of the virus are resistant to the new baloxavir.
  - **1/27/2019 According to the Japanese National Institute of Infectious Disease (NIID), baloxavir-resistant viruses were found in two of four primary school students in Yokohama in generic screenings in December** conducted after they developed flu symptoms earlier the same month.
  - **The mutated viruses were 76 to 120 times more resistant to the new anti-flu drug than unmutated ones** detected in the other two children.
  - **In clinical trials of baloxavir marboxil, resistant viruses were detected in 23.4 percent of participating patients younger than 12 years old.**

Low Dose Aspirin for Primary Prevention?

Effects of Aspirin for Primary Prevention in Persons with DM (ASCEND Study)

- Summary: Randomized trial **of 15,480 participants to enteric-coated aspirin at 100mg daily dose, or placebo in persons who had diabetes without cardiovascular disease, with a mean follow up of 7.4 years. Primary efficacy outcome was first serious vascular event and primary safety outcome was first occurrence of any major bleeding.**
- Criteria: ≥ 40 year old men and women with diagnosis of DM (any type)
- Exclusion Criteria: Clear indication for aspirin and had a past history of cardiovascular event
- Results:

*** Primary efficacy outcome: Aspirin group vs. placebo (8.5% vs. 9.6% P=0.01) NNT over 7.4 years: 91**

*** Primary safety outcome: Aspirin group vs. placebo (4.1% vs. 3.2% P=0.003) NNH over 7.4 yrs: 111**

***Aspirin use prevented cardiovascular events, but caused higher risks of major bleeding events, nearly in a 1:1 ratio!**

There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%])

published on August 26, 2018, at NEJM.org.

Effects of Aspirin on All-Cause Mortality in the Healthy Elderly (ASPREE Study)

- Summary: Randomized, placebo-controlled trial of **19,114 participants were assigned either 100mg of enteric-coated aspirin daily or placebo, with a median follow up of 4.7 years**. The primary end point was disability free survival and the primary composite end point was the first end-point events of death, dementia and persistent physical disability.
- Inclusion Criteria: **≥70 year old men and women (or ≥ 65 years old among black and Hispanics in the United States)**
- **Exclusion Criteria: Past history of cardiovascular event, dementia or disability**
- **Results:**

* **The risk of death from any cause was 12.7 events per 1000 persons-year in the aspirin group and 11.1 events per 1000 persons-years in the placebo group (hazard ratio, 1.14**; 95% CI, 1.01 to 1.29)

* **Cancer related deaths occurred in 3.1% of participants in aspirin group vs. 2.3% in placebo group (hazard ratio, 1.31**; 95% CI, 1.10 to 1.56) NNH:125

*Higher rates of mortality were observed among patients taking aspirin compared to the placebo

N Engl J Med 2018; 379:1499; 1509 and 1519

Use of Aspirin to Reduce Risk of Initial Vascular Events in Patients at Moderate Risk of Cardiovascular Disease (ARRIVE Study)

- Summary: Randomized, double-blinded, placebo controlled, multicenter study with **12,546 patients assigned to enteric-coated 100mg aspirin or placebo, with median follow up of 5 years. Primary end point was a composite outcome of time to first occurrence of CV death, MI, unstable angina, stroke or TIA.**
- Inclusion Criteria: **Men ≥55 years of age who had 2 to 4 risk factors and women ≥60 years of age, who had between 3 or more risk factors.**
- Exclusion Criteria: Patients with high risk for GI bleeding, diabetes, high risk for other bleeding and history of vascular event
- Results:

* **The primary endpoint occurred in 4.29% of patients in the aspirin group and 4.48% in the placebo group (hazard ratio 0.96, 95% CI, 0.81-1.13) *not statistically different!**

* **GI bleeding occurred in 0.97% of patients in the aspirin group vs. 0.46% in placebo group (hazard ratio, 2.11, 95% CI, 1.36-3.28), NNH over 5 years: 196**

*Aspirin treatment did not lower the risk of major cardiovascular events yet doubled the incidence of GI bleeds compared to placebo.

Lancet 2018; 392:1036.

Aspirin for Primary Prevention of Cardiovascular Disease and Cancer

- **"We no longer suggest that primary prevention with aspirin is appropriate for most patients over age 40, but now advise that the decision whether to use aspirin for primary prevention of cardiovascular disease and cancer be made based on shared decision-making, taking into account the probable benefits and harms of aspirin relative to the specific patient."**
- **"The balance between benefits and harms may weigh more heavily for harms over benefits in those over 70 years of age."**
- **"In secondary prevention of cardiovascular disease (CVD), the absolute benefits of aspirin on occlusive events are greater than the absolute harm of major bleeding."**
  - Current UpDate 28 November 2018 | Volume 5 | Issue 24

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

- "**Aspirin is well established for secondary prevention of ASCVD** and is widely recommended for this indication. However, **in primary prevention, aspirin use is more controversial**. Because persons without prior ASCVD are inherently less likely to have future ASCVD events than are those with a prior history, **it is more challenging for clinicians and patients to balance benefits and harms of prophylactic aspirin for primary prevention**. This uncertainty is reflected in international guidelines, where, for example, **aspirin is not recommended in European guidelines for primary ASCVD prevention but is recommended in prior U.S. guidelines for selected primary prevention for adults who have elevated risk of ASCVD based on traditional risk factors**. Adding to this controversy **are more recently conducted primary-prevention trials that, in contrast to older trials, have shown less overall benefit of prophylactic aspirin alongside co-administration of contemporary ASCVD preventive treatments, such as evidence-based hypertension and cholesterol therapies."**

Journal of the American College of Cardiology (2019), doi: https://doi.org/10.1016/j.jacc.2019.03.010

Inhaled Corticosteroid/Long Acting Beta Agonists

ICS/LABA Combination in Children?

- A multicenter trial **(VESTRI) randomly assigned 6208 children 4 to 11 years of age who had an asthma exacerbation in the previous year to a combination inhaler with fluticasone propionate (100 mcg or 250 mcg/inhalation) plus salmeterol (Advair) or to monotherapy with fluticasone propionate (100 mcg or 250 mcg/inhalation), one inhalation twice daily for 26 weeks.**
- **The number of patients who had a severe asthma exacerbation was 25% lower among children who continued taking fluticasone–salmeterol than among those who switched to fluticasone alone.**
- **Serious adverse events (hospitalization due to asthma exacerbation) occurred in 27 of 3107 patients in the fluticasone-salmeterol group and in 23 of the 3101 patients in the fluticasone group, hazard ratio 1.28 (95% CI 0.73-2.27). No deaths or endotracheal intubations were reported**. This hazard ratio suggests that the risk of serious asthma-related events was similar between the two groups.
  - N Engl J Med. 2016 Sep;375(9):840-9

ICS/LABA Combination in Adults/Adolescents

- **AUSTRI a multicenter, noninferiority trial, 11,679 adolescents (>/=12) and adults with persistent asthma were randomly assigned to take either inhaled fluticasone or the combination of inhaled fluticasone-salmeterol (Advair) for 26 weeks.** Combination therapy was administered using a single inhaler that contained both fluticasone and salmeterol.
- The **risk of a severe asthma exacerbation was 21% lower in the fluticasone-salmeterol group than in the fluticasone-only group** (hazard ratio, 0.79; 95% CI, 0.70 to 0.89),
- **The hazard ratio for a serious asthma-related adverse event in the fluticasone-salmeterol group compared with fluticasone alone was 1.03 (95% CI 0.64-1.66), suggesting no increased risk related to the addition of the LABA.** Furthermore, **no deaths occurred in either group**, and no difference was noted in the rate of asthma-related hospitalizations.
  - N Engl J Med. 2016;374(19):1822.

ICS/LABA Combination in Adults/Adolescents

- **The combination of budesonide (80 mcg or 160 mcg) plus formoterol (Symbicort) was compared with budesonide (80 mcg or 160 mcg) in a multicenter trial of 11,693 patients aged 12 and older** with one to four asthma exacerbations in the previous year; 2 inhalations were used twice daily for 26 weeks.
- The **risk of an asthma exacerbation was 16 percent lower in the budesonide-formoterol group.**
- A **serious asthma-related event occurred in 43 of 5846 patients in the combination arm and in 40 of 5847 in the budesonide arm, hazard ratio 1.07 (95% CI 0.70-1.65),** suggesting a similar risk between the groups.
  - N Engl J Med. 2016 Sep;375(9):850-60.

FDA Removes Boxed Warning From LABA/ICS Asthma/COPD Meds.

- **Dec 20, 2017 the FDA announced that asthma and COPD inhalers "delivering fixed-dose combinations of inhaled corticosteroid (ICS) and long-acting beta agonists (LABA) drugs will no longer be required to carry a boxed warning about the possibility of asthma-related death associated with their use."**
- The removal comes after an agency review of four large clinical safety trials showed "no increase in serious asthma-related side effects with the ICS/LABA fixed-dose products than with ICS agents alone." The trials also revealed "no significant increase in the risk for asthma-related hospitalizations, intubation, or asthma-related deaths associated with the combination treatment in adults and children."

ICS/LABA Combinations for Asthma

- **Advair Diskus**: fluticasone propionate & salmeterol BID **(asthma age 4 and older) 2015 US sales $4.7 billion (# 7 in US sales)**
- **Advair HFA** BID **(asthma age 12 and older)**
- **Symbicort**: budesonide & formotorol BID **(asthma age 6 and older)**
- **Dulara**: mometasone furoate and formoterol BID **(asthma age 12 and older)**
- **Breo Ellipta:** fluticasone furoate & vilanterol QD **(asthma age 18 and older)**
- **AirDuo Respiclick:** fluticasone propionate & salmeterol BID **(asthma age 12 and older)**
- **Several AB Rated Advair Diskus generics either have been approved (Mylan and GSK/Prasco) or awaiting FDA approval including Sandoz**

Fluticasone propionate and salmeterol inhalation - Wixela Inhub by Mylan

- January 30, 2019: Wixela Inhu is the **first FDA-approved therapeutically equivalent generic of Advair Diskus (twice daily fluticasone propionate and salmeterol inhalation powder) for certain patients 4 years and older with asthma or adults with chronic obstructive pulmonary disease (COPD). Expected availability by mid to late February 2019.**
- In the **28-day, randomized, double-blind, placebo-controlled, parallel group study of 1,128 adult asthma patients** conducted to evaluate the local (lung) **bioequivalence of Wixela Inhub 100 mcg/50 mcg and Advair Diskus 100 mcg/50 mcg, the two treatments produced equivalent efficacy. Both treatments were safe and well-tolerated** with lower numbers of withdrawals due to asthma compared to the placebo group.
- The treatment, the first generic of Advair, is approved in three doses and will be **priced between $93.71 and $153.14 (about 70% less)** the company said.

Fluticasone propionate and Salmeterol inhalation powder – Wixela Inhub Inhaler

Mylan's product (Wixela Inhub) is available in 3 strengths 100 mcg/50 mcg, 250 mcg/50 mcg and 500 mcg/50 mcg at wholesale acquisition costs (WACs) that are 70% less than Advair Diskus and 67% less than GSK's/Prasco's authorized generic. As of March 2019 Mylan has already achieved about a 25% market share.

$93.71 vs. Advair 100/50 - $345.00; $116.44 vs Advair 250/50 - $420.00; $153.14 vs. Advair 500/50 - $550.00

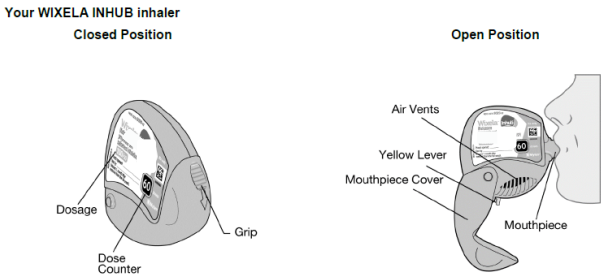
Fluticasone propionate and Salmeterol inhalation powder – Wixela Inhub Inhaler

- **As of April 19, 2019 Wixela Inhub Inhaler had already achieved a 28% market share** which is still climbing.
- **May 18, 2019 Mylan announced four scientific abstracts** from the Wixela™ Inhub™ (fluticasone propionate and salmeterol inhalation powder, USP) development program that will be **presented at the 2019 American Thoracic Society International Conference,** May 17 – May 22. The data, available for the first time publicly, further **supports the FDA's approval** in January 2019 of Mylan's Abbreviated New Drug Application for Wixela Inhub, which is indicated **for certain patients with asthma or chronic obstructive pulmonary disease (COPD).**

Fluticasone propionate and Salmeterol inhalation powder – Wixela Inhub Inhaler

- Abstract 11902: Pulmonary Therapeutic Bioequivalence of Wixela™ Inhub™ and Advair Diskus® in Adults With Asthma
- Abstract 12321: Usability and Robustness of the Wixela™ Inhub™ Dry Powder Inhaler
- Abstract 8715: Wixela™ Inhub™ Dry Powder Inhaler: In Vitro Performance Compared with Advair Diskus® and Inhalation Profiles in Patients with Asthma or Chronic Obstructive Pulmonary Disease
- Abstract 12048: Equivalent Systemic Exposure to Fluticasone Propionate/Salmeterol Following Single Inhaled Doses of Advair Diskus® and Wixela™ Inhub™: Results of 3 Pharmacokinetic Equivalence Studies

Fluticasone propionate and Salmeterol inhalation powder – Wixela Inhub Inhaler



Fluticasone propionate and Salmeterol powder Diskus

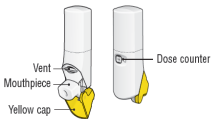
by Prasco Laboratories

Generic

Advair Diskus

Fluticasone propionate /Salmeterol inhalation powder AirDuo RespiClick

- **Fluticasone propionate/salmeterol xinafoate MDPI 118/13.2 mcg had similar clinical efficacy with lower systemic exposure when compared to the 50 mcg of salmeterol in fluticasone propionate/salmeterol 100/50 mcg dry powder inhaler**
- **AirDuo RespiClick has a yellow cap**
- **Instruct patients to not open their inhaler unless they are taking a dose. Repeated opening and closing the cover without taking medication will waste medication and may damage the inhaler.**
- Advise patients to **keep their inhaler dry** and clean at all times. **Never wash or put any part of the inhaler in water.**



Fluticasone propionate/Salmeterol Dry Powder RespiClick Inhalers by Teva

Air Duo Brand ~ $250.00

Generic Fluticasone/Salmeterol ~ $90.00

NOT generic or AB rated for Advair Diskus

Migraine Headache

- Migraine has a global prevalence of 15 to 18% and is a leading cause of disability worldwide.
- Chronic migraine (CM), occurring in approximately 2% of the population, has been defined as the occurrence of at least 15 days with headache per month for at least 3 months.
- Episodic migraine (EM), has been defined as 0 to 14 days with headache per month.
- The relationship between EM and CM is complex. EM progresses to CM at the rate of 2.5% per year, and CM often remits to EM (2-year transition rate of 26%).

Erenumab-aooe (Aimovig) by Amgen and Novartis

- **May 17, 2018 The U.S. Food and Drug Administration approved erenumab-aooe (Aimovig) for the preventive treatment of migraine in adults.** The treatment is given by **once-monthly self-injections**. Erenumab-aooe is the first FDA-approved preventive migraine treatment in **a new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule that is involved in migraine attacks.**
- **Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody. Erenumab is specific and selective to CGRP receptors, exerting action by full competitive inhibition of the receptor.**

Erenumab-aooe (Aimovig)

- Pharmacokinetics: Median **time to peak concentration after subcutaneous administration of erenumab 1 mg to 210 mg ranged from 4 to 11 days (mean ~ 6 days).**
- The **estimated elimination half-life of erenumab in a typical 70 kg person receiving erenumab 70 mg subcutaneously is approximately 21 days.**
- **Erenumab-aooe is not metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.**

Erenumab-aooe (Aimovig)

- **955 patients with a history of episodic migraines (with or without aura) for at least 12 months**
- **Primary End Point: Mean reduction in MMD from baseline was −3.2 days with erenumab 70 mg (P<0.001 vs placebo), −3.7 days with erenumab 140 mg (P<0.001 vs placebo), and −1.8 days with placebo during weeks 13 to 24. ~ 1 to 2 days reduction per month.**
- **Secondary End Point(s): Reduction in MMD of 50% or more was achieved by 43%, 50%, and 27% of patients in the erenumab 70 mg, erenumab 140 mg, and placebo groups**, respectively (P<0.001 for both erenumab groups vs placebo). **The number needed to treat was 6.3 for erenumab 70 mg versus placebo and was 4.4 for erenumab 140 mg versus placebo.**
- Exploratory patient-reported outcome values showed improvements from baseline in quality of life, disability, and migraine-related impact on life.
- **Erenumab adverse reactions and tolerability were similar to placebo.**
  - N Engl J Med 2017; 377:2123-2132

Erenumab-aooe (Aimovig)

Table 5: Efficacy Endpoints at Month 3 in Study 3

Chronic Migraine	AIMOVIG 70 mg Once Monthly N = 188	AIMOVIG 140 mg Once Monthly N = 187	Placebo N = 281
Monthly Migraine Days (MMD)			
Change from baseline	-6.6	-6.6	-4.2
Difference from placebo	-2.5	-2.5	
p-value	< 0.001	< 0.001	
≥ 50% MMD responders			
% Responders	39.9%	41.2%	23.5%
Difference from placebo	16.4%	17.7%	
Odds ratio relative to placebo	2.2	2.3	
p-value	< 0.001	< 0.001	
Monthly acute migraine-specific medication days			
Change from baseline	-3.5	-4.1	-1.6
Difference from placebo	-1.9	-2.6	
p-value	< 0.001	< 0.001	

The Lancet Neurology Volume 16, Issue 6, June 2017, Pages 425-434

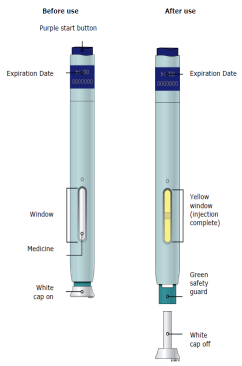
Erenumab-aooe (Aimovig)

The autoinjector should be stored refrigerated at 2° C to 8° C (36° F to 46° F) in the original carton to protect from light until time of use (do not freeze or shake). Cost $600.00 for 2 Sure Click

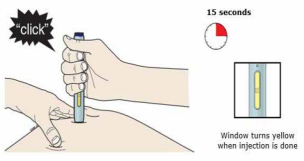
Leave the autoinjector at room temperature for at least 30 minutes before injecting. If removed from the refrigerator, the autoinjector can be kept at room temperature in the original carton up (up to 25°C [77°F]) for up to 7 days.

The needle shield within the white cap of the AIMOVIG prefilled autoinjector and gray needle cap of the prefilled syringe contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex.

Erenumab-aooe (Aimovig)



- Cost $600.00 for 2 SureClick autoinjector



Note: After you remove the autoinjector from your skin, the needle will be automatically covered.

Erenumab-aooe (Aimovig)

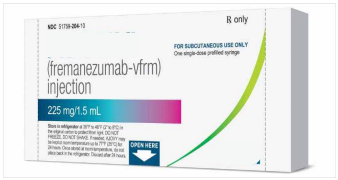
- In a **1-year open-label extension study in 451 patients with chronic migraine**, patients taking 140 mg and 70 mg of erenumab **experienced reductions of average monthly migraine days of 10.5 days and 8.5 days, respectively, compared to a baseline of 18.1 days. Patients treated with Aimovig experienced reductions in monthly migraine days of:**
- **50 percent or more: 67 percent on 140 mg and 53 percent on 70 mg**
- **75 percent or more: 42 percent on 140 mg and 27 percent on 70 mg**
- **100 percent reduction: 13 percent on 140 mg and 6 percent on 70 mg**
  - Amgen press release 6/28/2018

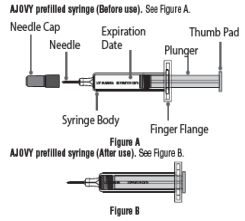
Fremanezumab-vfrm (Ajovy) by Teva

- **9/14/18 FDA approved Fremanezumab-vfrm for the prevention of migraines in adults.**
- **A fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand that binds to the CGRP ligand and blocks its binding to the receptor.** Fremanezumab-vfrm is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells.
- **Recommended Dosage**: Two subcutaneous dosing options of fremanezumab-vfrm are available to administer the recommended dosage:
  - **225 mg monthly, (available in 225 mg/1.5 mL single-dose prefilled syringe) or**
  - **675 mg every 3 months (quarterly), which is administered as three consecutive subcutaneous injections of 225 mg each. Cost ~$400.00/prefilled syringe**

Fremanezumab-vfrm (Ajovy)

- **Remove fremanezumab-vfrm/AJOVY from the refrigerator. Prior to use, allow the medication to sit at room temperature for 30 minutes protected from direct sunlight.** Do not warm by using a heat source such as hot water or a microwave. Do not use if it has been at room temperature for 24 hours or longer.





Fremanezumab-vfrm (Ajovy)

- **After single subcutaneous (SC) administrations of 225 mg, 675 mg, and 900 mg fremanezumabvfrm, median time to maximum concentrations (tmax) was 5 to 7 days.** Dose-proportionality, based on population PK, was observed between 225 mg to 900 mg. Steady state was achieved by approximately 168 days (about 6 months) following 225 mg SC monthly and 675 mg SC quarterly dosing regimens.
- **Fremanezumab-vfrm was estimated to have a half-life of approximately 31 days.**
- **Fremanezumab is not metabolized by cytochrome P450 enzymes;** therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Fremanezumab-vfrm (Ajovy)

Table 2: Efficacy Endpoints in Study 1

Study 1 Efficacy Endpoint Episodic Migraine	AJOVY 225 mg Monthly (N=287)	AJOVY 675 mg Quarterly (N=288)	Placebo (N=290)
Monthly migraine days (MMD)			
Baseline migraine days	8.9	9.2	9.1
Change from baseline	-3.7	-3.4	-2.2
Difference from placebo	-1.5	-1.2	
p-value	<0.001	<0.001	
≥50% MDD responders			
% responders	47.7%	44.4%	27.9%
Difference from placebo	19.8%	16.5%	
p-value	<0.001	<0.001	
Monthly acute migraine-specific medication days			
Change from baseline	-3.0	-2.9	-1.6
Difference from placebo	-1.4	-1.3	
p-value	<0.001	<0.001	

Figure 1 displays the mean change from baseline in the average monthly number of migraine days in Study 1.

Fremanezumab-vfrm (Ajovy)

- **Study 2** (NCT 02621931) included **adults with a history of chronic migraine (patients with ≥15 headache days per month).** All patients were randomized (1:1:1) **to receive subcutaneous injections of either fremanezumab 675 mg starting dose followed by 225 mg monthly, 675 mg every 3 months (quarterly), or placebo monthly, over a 3-month treatment period.** Patients were allowed to use acute headache treatments during the study. A subset of patients (21%) was allowed to use one additional concomitant, preventive medication.
- **1130 patients (991 females, 139 males), ranging in age from 18 to 70 years, were randomized. A total of 1034 patients completed the 3-month double-blind phase**.

Fremanezumab-vfrm (Ajovy)

Table 3: Efficacy Endpoints in Study 2

Study 2 Efficacy Endpoint Chronic Migraine	AJOVY 225 mg[a] Monthly (N=375)	AJOVY 675 mg Quarterly (N=375)	Placebo (N=371)
Baseline headache days of any severity[b]	20.3	20.4	20.3
Baseline headache days of at least moderate severity[c]	12.8	13.2	13.3
Change from baseline in the monthly average number of headache days of at least moderate severity	-4.6	-4.3	-2.5
Difference from placebo	-2.1	-1.8	
p-value	<0.001	<0.001	
Change from baseline in the monthly average number of migraine days in patients	-5.0	-4.9	-3.2
Change from baseline in monthly average number of headache days of at least moderate severity at 4 weeks after 1st dose	-4.6	-4.6	-2.3
Percentage of patients with ≥ 50% reduction in monthly average number of headache days of at least moderate severity	40.8%	37.6%	18.1%
Change from baseline in monthly average number of days of acute headache medication	-4.2	-3.7	-1.9

[a] In Study 2, patients received a 675 mg starting dose.
[b] Used for chronic migraine diagnosis.
[c] Used for primary endpoint analysis.

Fremanezumab-vfrm (Ajovy)

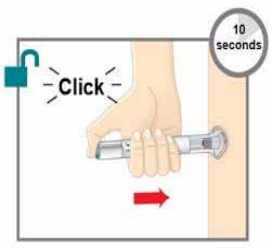
- In 3-month placebo-controlled studies, treatment-emergent ADA responses were observed in 6 out of 1701 (0.4%) fremanezumab-treated patients. One of the 6 patients developed anti-fremanezumab neutralizing antibodies at Day 84. **In the ongoing long-term open-label study, ADA were detected in 1.6% of patients (30 out of 1888). Out of 30 ADA-positive patients, 17 had a neutralizing activity in their post-dose samples.** Although these data do not demonstrate an impact of anti-fremanezumab-vfrm antibody development on the efficacy or safety of fremanezumab in these patients, the available data are too limited to make definitive conclusions.

Fremanezumab-vfrm (Ajovy)

- **The most common adverse reactions were at the injection site (eg, injection-site pain, injection-site erythema), and occurred in 47% of the group receiving fremanezumab quarterly, 47% of those receiving fremanezumab monthly, and 40% of the placebo group.** The most common adverse event was injection-site pain, which occurred in 30% of the fremanezumab quarterly group, 26% of the fremanezumab monthly group, and 28% of the placebo group
- **Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with fremanezumab in clinical trials.** Most reactions were mild to moderate, but some led to discontinuation or required corticosteroid treatment. Most reactions were reported from within hours to one month after administration.

Galcanezumab-gnlm (Emgality) by Lilly

- **9/27/18 FDA approved galcenezumab-gnlm for the prevention of migraines in adults. A humanized IgG4 monoclonal antibody specific for calcitonin-gene related peptide (CGRP) ligand and blocks its binding to the receptor. (Note-only the 120 mg dose after a loading dose of 240 mg is FDA approved)**



Galcanezumab-gnlm (Emgality)

Pharmacokinetics:

- **The time to maximum concentration is 5 days, and the elimination half-life is 27 days.**
- Galcanezumab-gnlm is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.
- The pharmacokinetics of galcanezumab-gnlm were **not affected by age, sex, race, or subtypes of migraine spectrum (episodic or chronic migraine**), based on a population pharmacokinetics analysis. **Body weight has no clinically relevant effect** on the pharmacokinetics of galcanezumab-gnlm.
- **Renal and hepatic impairment are not expected to affect the pharmacokinetics of galcanezumab-gnlm.**
- **Galcanezumab-gnlm is not metabolized by cytochrome P450 enzymes;** therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

Galcanezumab-gnlm (Emgality)

Table 2: Efficacy Endpoints in Studies 1 and 2

Episodic Migraine	Study 1		Study 2	
	EMGALITY 120 mg N = 210	Placebo N = 425	EMGALITY 120 mg N = 226	Placebo N = 450
Monthly Migraine Headache Days (over Months 1 to 6)				
Baseline migraine headache days	9.2	9.1	9.1	9.2
Mean change from baseline	-4.7	-2.8	-4.3	-2.3
Difference from placebo*	-1.9		-2.0	
≥50% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	62%	39%	59%	36%
≥75% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	39%	19%	34%	18%
100% Migraine Headache Days Responders (over Months 1 to 6)				
% Responders*	16%	6%	12%	6%
Monthly Migraine Headache Days that Acute Medication was Taken (over Months 1 to 6)				
Mean change from baseline (days)*	-4.0	-2.2	-3.7	-1.9
MSQ Role Function-Restrictive Domain Score (over Months 4 to 6)				
Baseline	51.4	52.9	52.5	51.4
Mean change from baseline[a]	32.4	24.7	28.5	19.7
Difference from placebo*	7.7		8.8	

[a] N = 189 for EMGALITY 120 mg and N = 377 for placebo in Study 1; N = 213 for EMGALITY 120 mg and N = 396 for placebo in Study 2.
* p<0.001

Galcanezumab-gnlm (Emgality)

- **Chronic Migraine: REGAIN Study 3** (NCT02614261) included **adults with a history of chronic migraine (≥15 headache days per month with ≥8 migraine days per month).** All patients were randomized in a 1:1:2 ratio to receive **once-monthly subcutaneous injections of Galcanezumab 120 mg, Galcanezumab 240 mg, or placebo over a 3-month treatment period. All patients in the 120 mg group received an initial 240 mg loading dose. (Note-only the 120 mg dose after a loading dose of 240 mg is FDA approved)**

Galcanezumab-gnlm (Emgality)

Table 3: Efficacy Endpoints in Study 3

Chronic Migraine	EMGALITY 120 mg N = 273	Placebo N =538
Monthly Migraine Headache Days (over Months 1 to 3)		
Baseline migraine headache days	19.4	19.6
Mean change from baseline	-4.8	-2.7
Difference from placebo*	-2.1	
≥50% Migraine Headache Days Responders (over Months 1 to 3)		
% Responders*	28%	15%

[B] N = 252 for EMGALITY 120 mg and N = 494 for placebo.
* p<0.001

Galcanezumab-gnlm (Emgality)

- **Adverse Effects: Injection site reactions (18% galcanezumab vs. 13% placebo)** include multiple related adverse event terms, such as injection site pain, injection site reaction, injection site erythema, and injection site pruritus.
- **Immunogenicity: With 12 months of treatment in an open-label study, up to 12.5% (16/128) of galcanezumab-treated patients developed anti-galcanezumab-gnlm antibodies, most of whom tested positive for neutralizing antibodies.**
- Although anti-galcanezumab-gnlm antibody development was **not found to affect the pharmacokinetics, safety, or efficacy of galcanezumab in these patients, the available data are too limited to make definitive conclusions.**

Galcanezumab-gnlm – Emgality

- March 2019 the Food and Drug Administration **"granted Priority Review for the supplemental Biologics License Application (sBLA) for galcanezumab (Emgality) for the prevention of episodic cluster headache in adults."** The article explains that the sBLA "is supported by data from a phase 3 study of patients with episodic cluster headache."

Inhaled Levodopa – Inbrija by Acorda Therapeutics

- Inbrija (in-BRIH-jah) is the first INHALED levodopa for adults with Parkinson's disease.
- Think of Inbrija as a fast-acting dose of levodopa. It joins Apokyn (apomorphine) injection...the only other "rescue" option.
- **Inbrija works in about 10 minutes...and lasts about an hour.**
- **It will be used to treat "off-time"...when scheduled meds wear off early or kick-in late and symptoms (rigidity, tremor, etc) worsen. Up to 90% of Parkinson's patients have these symptoms after 10 years of therapy.**
- But **Inbrija won't REPLACE daily meds**. Patients will still need scheduled carbidopa/levodopa...and may also use add-ons such as dopamine agonists (pramipexole, etc), MAO-B inhibitors (rasagiline, etc) or COMT inhibitors (entacapone, etc).
- And it's **a specialty med costing about $32/dose...less than Apokyn at about $200/dose.**

Inhaled Levodopa – Inbrija

- Plus **each dose of Inbrija's requires loading the inhaler with a capsule...inhaling...removing the cap...and repeating. This could be difficult for some patients with Parkinson's disease.**
- **Optimize carbidopa/levodopa schedules and add-on meds to minimize off-time...BEFORE considering Inbrija.**
- For example, **use lower doses of carbidopa/levodopa more often...or a longer-acting option (Rytary, etc).**
- Save Inbrija for patients with unpredictable off-time episodes...or when other med adjustments don't do the trick.
- **Tell patients Inbrija may lead to cough...but early evidence doesn't suggest changes in lung function**.
- But **don't use Inbrija in patients with COPD, asthma, or other respiratory diseases...due to the risk of bronchospasm.**

Inhaled Levodopa – Inbrija

Dosing
One dose (84 mg) = two 42-mg capsules
No more than 1 dose per OFF period
May be taken as needed **up to a maximum of 5x per day when symptoms start to return**
Average number of doses in clinical trials: ~2 per day
Important Administration Instructions
For oral inhalation only; INBRIJA capsules must not be swallowed as intended effect would not be obtained
INBRIJA capsules are only for use with the INBRIJA inhaler
Effective only in combination with CD/LD
Capsules should be stored in their blister package and only removed immediately before use

Demonstrated **Usability 99.8% (628/629) of randomized patients in the 2 clinical trials demonstrated the ability to self-administer INBRIJA while in an OFF period after instruction**

Inhaled Levodopa – Inbrija

- **If you have recurring or sporadic "off" times, you may want to consider Inbrija.** But because this is an add-on medication, it may be helpful to first ensure your current treatment is working as well as it can. Adjustments to how and when you take your medications could lessen "off" time.
- **For some people, separating levodopa from high-protein meals (meat, fish, nuts or beans, for example) by 30 to 60 minutes may ease symptoms. Levodopa and dietary protein are absorbed in the same part of the gut. When you take medication and protein at the same time, less medication may be absorbed, potentially leading to "off" time.**

Inhaled Levodopa – Inbrija

- **Changing your medication's dose or timing also may help. If your symptoms start to return gradually about an hour before every levodopa dose, for example, your doctor may recommend you take it more often or increase the dose, or add a longer-acting PD drug to prevent "wearing off."**
- **If you still have "off" time despite dietary and medication adjustments, Inbrija may be an option. Even for those whose symptoms are fairly well controlled, it may be good to have a rescue therapy on hand just in case "off" time comes on at an unpredictable or inconvenient moment.**

Cannabidiol Oral Solution (CBD-OS)– Epidiolex C-V by GW Research Labs

- **The IND for CBD-OS was submitted in 2014, and it was granted Orphan Drug Status and a Rare Pediatric Designation for the treatment of Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) and Fast-Track Designation for DS.**
- **FDA approved 6/25/2018 but the DEA has 90 days to determine what Schedule the medication will be.**
- **Schedule V by the DEA (9/27/2018) - Schedule V drugs are said to represent little potential for abuse.**
- The efficacy of CBD-OS was assessed in 3 Phase 3 Clinical Trails: 2 in LGS (study 1414 and 1423) and 1 in DS (Study 1332B).

Lennox-Gastaut syndrome and Dravet syndrome

- **Lennox-Gastaut syndrome begins in childhood. It is characterized by multiple types of seizures. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5.** More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably. **Almost all children with Lennox-Gastaut syndrome develop learning problems and intellectual disability. Many also have delayed development of motor skills such as sitting and crawling. Most people with Lennox-Gastaut syndrome require help with usual activities of daily living.**
- **Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent fever-related seizures (febrile seizures). Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms). Additionally, status epilepticus, a potentially life-threatening state of continuous seizure activity requiring emergency medical care, may occur. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity and difficulty relating to others.**

Cannabidiol Oral Solution (CBD-OS)– Epidiolex

- **Almost all patients with LGS and DS continue to have seizures despite treatment with multiple AEDs, putting them at high risk for injury or death. The primary goal of therapy for LGS and DS is to reduce seizure frequency and severity while limiting the AEs associated with multiple AEDs; however, there remains a significant unmet need for additional therapies for these patients.**

Cannabidiol Oral Solution (CBD-OS)– Epidiolex

- **Although CBD is a cannabinoid, it shares almost none of the pharmacologic features of the prototypical cannabinoid, Δ9-tetrahydrocannabinol (THC). In animal models of seizures, CBD is thought to exert its anticonvulsant effect by a reduction in neuronal hyperexcitability and inflammation** through modulation of intracellular calcium via the orphan G protein-coupled receptor (GPR55) and the transient receptor potential channel 1 (TRPV1), as well as through modulation of adenosine-mediated signaling.

Cannabidiol Oral Solution (CBD-OS)– Epidiolex C-V

Pharmacokinetics:

- **Adminstration with a high-fat/high-calorie meal increased Cmax by 5-fold, AUC by 4-fold, and reduced the total variability, compared with the fasted state in healthy volunteers**
- **Accumulation after multiple b.i.d. dosing of CBD-OS was moderate, with a CBD t½ of 60 hours (range 56-61 hours).**
- Despite the long terminal t½, steady state was reached within 2-4 days for parent drug CBD, based on trough values, likely reflecting that the terminal elimination was only a minor contributor to drug clearance.
- **Cannabidiol is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes**, and UGT1A7, UGT1A9, and UGT2B7 isoforms.

Cannabidiol Oral Solution (CBD-OS)– Epidiolex C-V

- **Potential Drug Interactions:**
  - **Moderate or strong inhibitors of CYP3A4 or CYP2C19 may increase CBD plasma levels and result in a greater risk of adverse effects, consider a reduction in CBD-OS dose when coadministered.**
  - **Moderate or strong inducers of CYP3A4 or CYP2C19 may decrease CBD plasma levels and reduce the efficacy, consider an increase in CBD-OS dosage when coadministered.**
  - **Diazepam and clobazam are both CYP2C19 substrates that are increased by coadministration of CBD-OS consider a dosage reduction.**
  - **Valproate and CBD-OS coadministration increases the risk of elevation of transaminases and may need to reduce dosage of CBD-OS.**

Table 4: Change in Drop Seizure Frequency in Lennox–Gastaut Syndrome during the Treatment Period (Studies 1 and 2)

Drop Seizure Frequency (per 28 Days)	Placebo	EPIDIOLEX 10 mg/kg/day	EPIDIOLEX 20 mg/kg/day
Study 1	**N=85**	**N/A**	**N=86**
Baseline Period Median	75	N/A	71
Median Percentage Change During Treatment	-22	N/A	-44
p-value compared to placebo			0.01
Study 2	**N=76**	**N=73**	**N=76**
Baseline Period Median	80	87	86
Median Percentage Change During Treatment	-17	-37	-42
p-value compared to placebo		<0.01	<0.01

Figure 2: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Lennox–Gastaut Syndrome (Study 2)

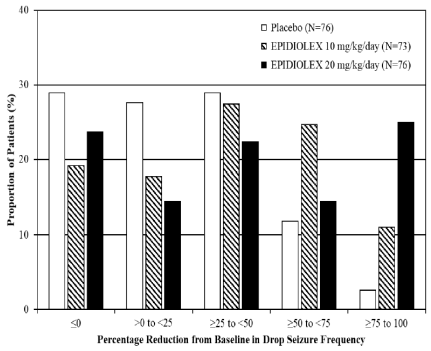
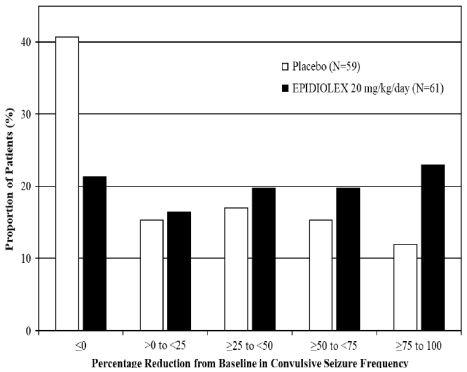


Table 5: Change in Convulsive Seizure Frequency in Dravet Syndrome during the Treatment Period (Study 3)

Total Convulsive Seizure Frequency (per 28 Days)	Placebo	EPIDIOLEX 20 mg/kg/day
Study 3	N=59	N=61
Baseline Period Median	15	12
Median Percentage Change During Treatment	-13	-39
p-value compared to placebo		0.01

Figure 3: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Dravet Syndrome (Study 3)



Adverse Reactions	EPIDIOLEX 10 mg/kg/day N=75 %	EPIDIOLEX 20 mg/kg/day N=238 %	Placebo N=227 %
Hepatic Disorders			
Transaminases elevated	8	16	3
Gastrointestinal Disorders			
Decreased appetite	16	22	5
Diarrhea	9	20	9
Weight decreased	3	5	1
Gastroenteritis	0	4	1
Abdominal pain, discomfort	3	3	1
Nervous System Disorders			
Somnolence	23	25	8
Sedation	3	6	1
Lethargy	4	8	2
Fatigue, malaise, asthenia	11	12	4
Insomnia, sleep disorder, poor quality sleep	11	5	4
Irritability, agitation	9	5	2
Aggression, anger	3	5	<1
Drooling, salivary hypersecretion	1	4	<1
Gait disturbance	3	2	<1
Infections			
Infection, all	41	40	31
Infection, viral	7	11	6
Pneumonia	8	5	1
Infection, fungal	1	3	0
Infection, other	25	21	24
Other			
Rash	7	13	3
Hypoxia, respiratory failure	3	3	1

Table 30: Frequency of ALT Elevations for Patients Taking or Not Taking Concomitant VPA in Pivotal Studies

Multiple of ULN for ALT	Concomitant VPA	Placebo (N=220) n / N (%)	CBD-OS 10 mg/kg/day (N=67) n / N (%)	CBD-OS 20 mg/kg/day (N=229) n / N (%)
>ULN	Yes	13/82 (15.9)	12/20 (60.0)	62/87 (71.3)
	No	19/93 (20.4)	7/36 (19.4)	22/90 (24.4)
>2×	Yes	4/95 (4.2)	2/23 (8.7)	44/104 (42.3)
	No	4/119 (3.4)	2/44 (4.5)	9/120 (7.5)
>3×	Yes	1/97 (1.0)	1/23 (4.3)	31/106 (29.2)
	No	1/122 (0.8)	0/44	6/121 (5.0)
>5×	Yes	1/97 (1.0)	1/23 (4.3)	14/106 (13.2)
	No	1/123 (0.8)	0/44	3/123 (2.4)
>8×	Yes	1/97 (1.0)	1/23 (4.3)	6/106 (5.7)
	No	0/123	0/44	0/123
>10×	Yes	1/97 (1.0)	0/23	3/106 (2.8)
	No	0/123	0/44	0/123
>20×	Yes	1/97 (1.0)	0/23	1/106 (0.9)
	No	0/123	0/44	0/123

Note: Due to its short duration, the 3-week pilot placebo-controlled study in DS (Study 1332 Part A) was not included in this analysis.
Note: N corresponds to the total number of patients in the treatment group. *n / N*: *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at baseline.

Prior to starting treatment with EPIDIOLEX, obtain serum transaminases (ALT and AST) and total bilirubin levels. Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with EPIDIOLEX, and periodically thereafter or as clinically indicated. Serum transaminases and total bilirubin levels should also be obtained within 1 month following changes in EPIDIOLEX dosage and addition of or changes in medications that are known to impact the liver. Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline.

Cannabidiol Oral Solution (CBD-OS)– Epidiolex C-V

- Warnings and Precautions:
  - Hepatocellular injury: monitor ALT, AST and bilirubin.
  - **Somnolence and sedation: tends to be dose related and transient** and is additive to other CNS depressants.
  - **Suicidal ideation and behavior: as with other anticonvulsants monitor patients for suicidal thoughts and behavior.**
  - **Withdrawal of antiepileptic medications: gradually reduce dose over time to reduce risk of increased seizure frequency and/or status epilepticus.**
  - **Hypersensitivity reactions: including pruritis, erythema or angioedema** (avoid in patients who are sensitive to cannabidiol or any ingredient including **sesame oil**).

Cannabidiol Oral Solution (CBD-OS)– Epidiolex

Indications: treatment of seizures in patients with Lennox-Gastaut syndrome or Dravets syndrome in patients two years of age or older.
Available as 100 mg/ml in 100 ml clear/yellowish solution, expires 12 weeks after opening

Dosage Information

- EPIDIOLEX is to be administered orally.
- The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day).
- After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
- Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.

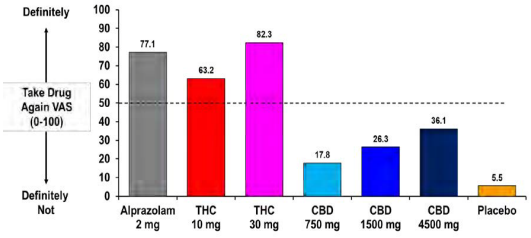
When taken with high fat/high calorie food the C-max is increased 5 fold and the AUC is increased 4 fold.

Cannabidiol Oral Solution (CBD-OS)– Epidiolex

Table 1: Dose Adjustments in Patients with Hepatic Impairment

Hepatic Impairment	Starting Dosage	Maintenance Dosage	Maximum Recommended Dosage
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)

Mean Drug Take Drug Again Visual Analogue Scale Scores by Treatment (Completer Population)



The human data from clinical studies show that, following the abrupt cessation of CBD-OS in patients in the clinical trial setting, no signals of physical dependence were detected according to the Cannabis Withdrawal Scale or Pediatric Cannabinoid Withdrawal Scale.

From FDA Briefing Document 4-19-2018

Cannabidiol Oral Solution (CBD-OS)– Epidiolex

- **This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome.**
- CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the "high") that comes from tetrahydrocannabinol (THC).
- **It is THC (and not CBD) that is the primary psychoactive component of marijuana.**
- **Should be available by mid November 2018 now that DEA has scheduled the drug as a C-V.**

Cannabidiol Oral Solution (CBD-OS)– Epidiolex C-V

- EPIDIOLEX is a **strawberry flavored clear, colorless to yellow solution supplied in a 105 mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution** (NDC 70127-100-01). **Each mL contains 100 mg of cannabidiol.** EPIDIOLEX is packaged in a carton with two 5 mL calibrated oral dosing syringes and a bottle adapter (NDC 70127-100-10). The pharmacy will provide 1 mL calibrated oral dosing syringes when doses less than 1 mL are required.
- **Cost: $32,500/year**

Non-FDA Approved CBD Extracts

- A 2017 study published in the Journal of the American Medical Association, researchers **tested 84 products purchased from 31 different online CBD sellers.** Roughly **seven out of 10 items had different levels of CBD than what was written on the label**. Of all of the items they tested, **roughly half of the items had more CBD than was indicated; a quarter had less. And 18 of the samples tested positive for THC, despite it not being listed on the label.**
- These findings highlight the need for manufacturing and testing standards, and oversight of medicinal cannabis products.
  - JAMA. 2017;318(17):1708-1709.

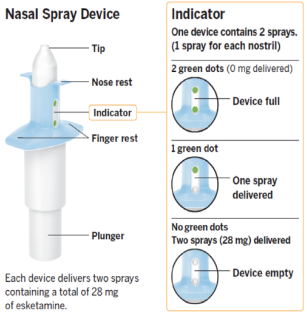
Esketamine Nasal Spray (Spravato) for Treatment Resistant Depression

- **2/12/2019 Two FDA advisory panels**, with 17 voting members, including psychiatrists and consumer representatives, was nearly unanimous **(14 yes, 2 no and 1 abstention) in deciding that the drug's benefits outweighed its risks.** The FDA typically follows the recommendations of its expert panels.
- **Esketamine is the S-enantiomer of ketamine, an FDA-approved anesthetic** and **street drug (Special K) known for its dissociative and hallucinogenic effects**. While **ketamine has not been approved for depression in the U.S. or any other country, it has been used off-label in cases of severe depression.**
- Unlike other antidepressants, its **onset of action can be extremely rapid -- within hours -- as opposed to several weeks for standard agents.**
- **Janssen announced that esketamine nasal spray will be known as Spravato. An FDA approval of March 5, 2019 as a C-III controlled substance.**

Esketamine Nasal Spray (Spravato) C-III

FDA Approved Indication:

- **a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults.**
- The nasal spray device delivers a total of 28 mg of esketamine. To prevent loss of medication, **do not prime the device before use. Use 2 devices (for a 56 mg dose) or 3 devices (for an 84 mg dose), with a 5-minute rest between use of each device to allow the medication to be absorbed.**



Esketamine Nasal Spray (Spravato)

Recommended Dosage for Adults **(Monitor patients for at least two hours after each administration)**

- **Induction Phase Weeks 1 to 4: Administer twice per week**
  - **Day 1 starting dose: 56 mg, Subsequent doses: 56 mg or 84 mg**
- **Maintenance Phase Weeks 5 to 8: Administer once weekly**
  - **56 mg or 84 mg**
- **Week 9 and after: Administer every 2 weeks or once weekly***
  - **56 mg or 84 mg**

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

Esketamine Nasal Spray (Spravato)

- **The time to reach maximum esketamine plasma concentration is 20 to 40 minutes after the last nasal spray of a treatment session.**
- After Cmax was reached following intranasal administration, the decline in plasma esketamine concentrations was biphasic, with rapid decline for the initial 2 to 4 hours and a **mean terminal half-life (t1/2) that ranged from 7 to 12 hours.**
- Esketamine is primarily metabolized to noresketamine metabolite via cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19.
- **Drug-drug interactions are not clinically significant.**

Esketamine Nasal Spray (Spravato) C-III

- Esketamine is designed to be administered intranasally twice a week for an initial 4 weeks, in conjunction with a newly initiated oral antidepressant. The proposed initial adult esketamine dose is 28-56 mg at each administration, which can be titrated to 84 mg by week 2. The drugmaker proposed continuing treatment weekly for 4 more weeks, and then weekly or every other week in an ongoing maintenance phase.
- The drug's side effect profile was of concern: in trials, **patients experienced sedation (49-61%), rising blood pressure, increased risk of suicidal thoughts and behaviors and dissociative sensations (61-75%), which are known effects of ketamine**. The latter effect, in fact, has made ketamine a popular street drug.

Esketamine Nasal Spray (Spravato)

- **Approximately 8% to 17% of esketamine-treated patients** and 1% to 3% of placebo-treated patients **experienced an increase of more than 40 mmHg in systolic BP and/or 25 mmHg in diastolic BP in the first 1.5 hours after administration** at least once during the first 4 weeks of treatment.
- **Instruct patients not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep. Patients will need to arrange transportation home following treatment with esketamine.**

Esketamine Nasal Spray (Spravato) C-III

- Three adverse events were particularly concerning: **sedation, dissociation, and increased blood pressure. The majority of these events happened during the first 2 hours after drug administration, and the FDA is recommending an REMS to ensure patient safety when using esketamine.**
- The **REMS would require esketamine to only be given in "certain healthcare settings where the patient could be monitored for 2 hours after administration, the drug would not be dispensed directly to patients, and patients would be enrolled in a registry to better characterize the risks associated with esketamine administration."**

Esketamine Nasal Spray (Spravato) C-III

- **Abuse potential: esketamine may produce a variety of symptoms including anxiety (31%), dysphoria, disorientation (41%), euphoria (4%),insomnia, flashback, hallucinations, and feelings of floating, detachment and to be "spaced out".** Monitoring for signs of abuse and misuse is recommended.
- A higher rate of lower urinary tract symptoms (**urinary frequency (3%)**, dysuria, micturition urgency, nocturia, and cystitis) in esketamine treated patients than in placebo-treated patients.
- Other **common side effects include: dizziness (29%), nausea (28%), vertigo (23%), headache (20%), dysgeusia (19%) and vomiting (9%).**

Esketamine Nasal Spray (Spravato) C-III

- A randomized, placebo-controlled, double-blind, multicenter, **short-term (4-week), Phase 3 study (Study 1; NCT02418585) in adult patients 18 to <65 years old with treatment-resistant depression (TRD)**. Patients in Study 1 met DSM-5 criteria for major depressive disorder (MDD) and in **the current depressive episode, had not responded adequately to at least two different antidepressants of adequate dose and duration.** After discontinuing prior antidepressant treatments, **patients in Study 1 were randomized to receive twice weekly doses of intranasal esketamine (flexible dose; 56 mg or 84 mg) or intranasal placebo. All patients also received open-label concomitant treatment with a newly initiated daily oral antidepressant (AD) (duloxetine, escitalopram, sertraline, or extended-release venlafaxine** as determined by the investigator based on patient's prior treatment history). Esketamine could be titrated up to 84 mg starting with the second dose based on investigator discretion.

Montgomery–Åsberg Depression Rating Scale - Interpretation

The physician-rated MADRS measures these 10 core symptoms of depression.
•MADRS is a widely used, physician-rated scale for assessing the severity of depressive symptoms.
•Each of the 10 symptoms on the MADRS is rated on a scale of 0-6; higher numbers denote greater severity of symptoms

•Apparent Sadness	•Reported Sadness
•Inner Tension	•Reduced Sleep
•Reduced Appetite	•Concentration Difficulties
•Lassitude	•Inability to Feel
•Pessimistic Thoughts	•Suicidal Thoughts

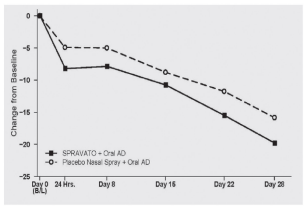
Usual cutoff points are:
0 to 6 – normal /symptom absent
7 to 19 – mild depression
20 to 34 – moderate depression
>34 – severe depression (Range 0 to 60)

Esketamine Nasal Spray (Spravato) C-III

Table 8: Primary Efficacy Results for Change from Baseline in MADRS Total Score at Week 4 in Patients with TRD in Study 1 (MMRM)

Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean (SE) Change from Baseline to end of Week 4	LS Mean Difference (95% CI)*
SPRAVATO (56 mg or 84 mg) + Oral AD†	114	37.0 (5.7)	-19.8 (1.3)	-4.0 (-7.3; -0.6)
Placebo nasal spray + Oral AD	109	37.3 (5.7)	-15.8 (1.3)	-

Figure 4: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Patients with TRD in Study 1* (Full Analysis Set) – MMRM Analysis



The **primary efficacy measure was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. The MADRS is a ten-item, clinician rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression. MADRS Score >34 – severe depression**

* Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO dosage from 84 mg to 56 mg twice weekly.

Onset of action is typically within hours to a day vs. weeks for FDA approved antidepressants

Esketamine Nasal Spray (Spravato) C-III

- **Five phase 3 studies in support of the TRD development program for esketamine.** The phase 3 studies include two short-term, double-blind, placebo-controlled studies—one fixed-dose and one flexible dose—in adult patients younger than 65 years of age; one short-term, double-blind, placebo controlled, flexible-dose study in geriatric patients > 65 years of age; one randomized withdrawal design study; and one long-term, open-label safety study.
- **Patients in all of these studies had failed at least two prior antidepressant trials and, at study entry, had more severe symptoms on average than patients entering antidepressant trials for previously approved drugs.** Thus, rather than randomizing severely ill patients to placebo alone, **each study involved the addition of a new antidepressant at the same time that either esketamine or placebo was initiated, ensuring that all patients were receiving some form of active treatment.**

Esketamine Nasal Spray (Spravato) C-III

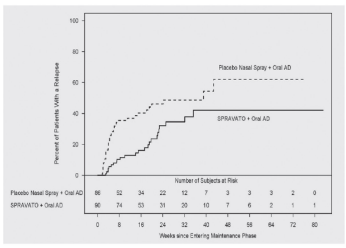
Treatment-Resistant Depression – Long-term Study

- Study 2 (NCT02493868) was a long-term randomized, double-blind, parallel-group, **multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remitters and responders to esketamine.** Patients in this study were responders in one of two short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexibly dosed esketamine (56 mg or 84 mg twice weekly) plus daily oral AD in an initial 4-week phase. **Stable remission was defined as a MADRS total score ≤ 12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction ≥ 50% for at least 3 of the last 4 weeks and not in remission. After at least 16 initial weeks of treatment with esketamine and an oral AD, stable remitters and stable responders were randomized separately to continue intranasal treatment with esketamine or switch to placebo nasal spray, in both cases with continuation of their oral AD**

Esketamine Nasal Spray (Spravato) C-III

- The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse.

Figure 5: Time to Relapse in Patients with TRD in Stable Remission in Study 2* (Full Analysis Set)

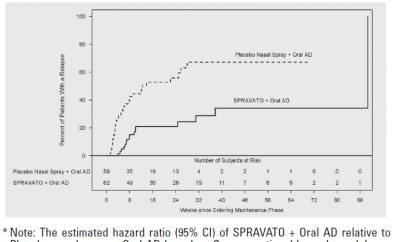


* Note: The estimated hazard ratio (95% CI) of SPRAVATO + Oral AD relative to Placebo nasal spray + Oral AD based on weighted estimates was 0.49 (95% CI: 0.29, 0.84). However, the hazard ratio did not appear constant throughout the trial.

Esketamine Nasal Spray (Spravato) C-III

In Study 2, based on depressive symptomatology, the majority of stable remitters (69%) received every-other-week dosing for the majority of time during the maintenance phase; 23% of stable remitters received weekly dosing. Among stable responders, 34% received every-other-week dosing and 55% received weekly dosing the majority of time during the maintenance phase. Of the patients randomized to SPRAVATO, 39% received the 56 mg dose and 61% received the 84 mg dose

Figure 6: Time to Relapse in Patients in Stable Response in TRD Patients in Study 2* (Full Analysis Set)



* Note: The estimated hazard ratio (95% CI) of SPRAVATO + Oral AD relative to Placebo nasal spray + Oral AD based on Cox proportional hazards model was 0.30 (95% CI: 0.16, 0.55).

Esketamine Nasal Spray (Spravato) C-III

Esketamine is available only through a restricted program called the **SPRAVATO REMS**. Inform the patient of the following notable requirements:

- Patients must be enrolled in the SPRAVATO REMS Program prior to administration.
- **Esketamine must be administered under the direct observation of a healthcare provider and healthcare settings must be certified in the program.**
- **Patients must be monitored by a healthcare provider for at least 2 hours after administration of esketamine.**
- **Pharmacies must be certified in the REMS and must only dispense esketamine to healthcare settings that are certified in the program.** Also available from selected Specialty Pharmacies including:
  - Cardinal Health Specialty Distribution; CuraScript Specialty Distribution; McKesson Specialty Health and Besse Medical

Esketamine Nasal Spray – Spravato C-III

Available as:

- A 56 mg Dose Kit: Unit-dose carton containing two 28 mg nasal spray devices (56 mg total dose)
- A 84 mg Dose Kit: Unit-dose carton containing three 28 mg nasal spray devices (84 mg total dose)
- Cost: **wholesale cost of each treatment with esketamine will range from $590 to $885, depending on the dose. That means twice-weekly treatments during the first month will cost centers that offer the drug at least $4,720 to $6,785.** Subsequent weekly treatments will cost about half as much.
- **Approximately one-third of people who have major depressive disorder (MDD) have not responded adequately to at least two different antidepressants of adequate dose and duration in the current depressive episode and are considered to have treatment resistant depression (TRD).**
- Fluoxetine plus Olanzapine (Symbyax) is the only other medication FDA approved for treatment resistant depression.

Esketamine Nasal Spray (Spravato) C-III

- **"Doctors welcomed federal approval this week of a new, fast-acting nasal spray for depression. But also they expressed concerns about its cost and long-term effects, as well as the logistics of administering it in accordance with safety requirements."** (New York Times 3/8/2019)
- In a move that may help thousands of former service members with depression that has not improved with other treatments, **VA officials announced 3/19 that the department's doctors are now authorized to prescribe Spravato.**

Esketamine Nasal Spray (Spravato) C-III

- **4/3/2019 Anxiety and Depression Association of American (ADAA) 2019 Conference, experts debated the drug's merits and potential pitfalls.**
- Weighing in on the side of caution, keynote **speaker Alan Schatzberg, MD, professor of psychiatry and behavioral sciences at Stanford University, "I'm more worried now than I was two years ago," he said. "We need to get phase 4 data looking at the effects when people stop ketamine treatment at different time points because right now, I don't think the concerns on this have been answered."**

Esketamine Nasal Spray (Spravato) C-III

- **"There appears to be a sharp relapse rate. Even after 12 to 16 weeks of treatment with esketamine, patients relapse quickly,"** he said.
- This relapse rate is documented in FDA files even though patients remained on the antidepressant medications they had been taking before and during the study.
- **"Even the antidepressant wasn't sufficient to prevent the relapse after discontinuing esketamine," said Schatzberg. "This represents a real problem. What are you going to do with these patients — tell them to keep taking the esketamine?"**

Esketamine Nasal Spray (Spravato) C-III

- FDA briefing documents submitted to advisory panels considering the **esketamine's approval report six deaths in patients with resistant depression and three suicides — two at 12 and 20 days after the last dose of esketamine, and one 4 days after the last dose.**
- Schatzberg and his team recently published a study showing that **ketamine's antidepressant effects require activation of opioid receptors in the brain as naltrexone given prior to IV ketamine attenuate the antidepressant effects of ketamine while the dissociative effects of ketamine are not mediated by the opioid system. This contradicts previous beliefs that the drug's effects primarily stem from its impact on the glutamate system.** (Am J Psychiatry 2018; 175:1205–1215)

Esketamine Nasal Spray (Spravato) C-III

- **Expect a very limited role for Spravato.**
- It's a C-III that patients can only get at a REMS-certified clinic or hospital...due to misuse and abuse risk. And they must be monitored for at least 2 hours after EACH dose...due to increased BP, sedation, dissociative effects, etc.
- Plus it costs up to $900 per dose. **Expect insurers to apply stringent criteria and require prior auths.**
- **Save Spravato as a last-line option for resistant depression...such as for patients not responding to AT LEAST 2 optimized regimens.**
- Be aware that **Spravato may not show up in your Rx drug monitoring program (PDMP)...meds given in the hospital or an outpatient clinic don't have to be reported to the PDMP.**
- Document Spravato use in the EHR...to identify drug interactions. For example, **using Spravato with CNS depressants (benzos, opioids, etc) may increase sedation...or stimulants (methylphenidate, etc) may raise BP.**

Brexanolone IV – Zulresso by Sage Therapeutics

- 3-19-2019 **First FDA approved medication for post-partum depression (PPD), priority review and breakthrough status, risk evaluation and mitigation strategy (REMS) required and pending scheduling as a controlled substance by DEA.**
- Brexanolone's mechanism of action is different from that of currently available antidepressants. It is **chemically identical to endogenous allopregnanolone, a hormone that decreases after childbirth. Brexanolone acts as a positive allosteric modulator of gamma-aminobutyric acid-A (GABAA) receptors, which become dysregulated in the postpartum period.**

Brexanolone IV – Zulresso

BOX WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

- Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO.
- **Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).**
- ZULRESSO is available only through a restricted program called the ZULRESSO REMS.

Brexanolone IV – Zulresso

DOSAGE AND ADMINISTRATION

- **A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion.**
- **Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:**
  - **0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour**
  - **4 to 24 hours: Increase dosage to 60 mcg/kg/hour**
  - **24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)**
  - **52 to 56 hours: Decrease dosage to 60 mcg/kg/hour**
  - **56 to 60 hours: Decrease dosage to 30 mcg/kg/hour**

Brexanolone IV – Zulresso

WARNINGS AND PRECAUTIONS

- Suicidal Thoughts and Behaviors: Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose PPD becomes worse or who experience emergent suicidal thoughts and behaviors.
- **If excessive sedation occurs at any time during the infusion, stop the infusion until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.**
- **Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.**

Brexanolone IV – Zulresso

Table 2 Adverse Reactions in Placebo-Controlled Studies in Patients with PPD Reported in ≥ 2% of ZULRESSO-Treated Patients and Greater than Placebo-Treated Patients

	Placebo (n=107)	Maximum dosage 60 mcg/kg/hour (n=38)	Maximum dosage 90 mcg/kg/hour (Recommended dosage) (n=102)
Cardiac Disorders			
Tachycardia	-	-	3%
Gastrointestinal Disorders			
Diarrhea	1%	3%	2%
Dry mouth,	1%	11%	3%
Dyspepsia	-	-	2%
Oropharyngeal pain	-	3%	2%
Nervous System Disorders			
Dizziness, presyncope, vertigo	7%	13%	12%
Loss of consciousness	-	5%	3%
Sedation, somnolence	6%	21%	13%
Vascular Disorders			
Flushing, hot flush	-	5%	2%

Brexanolone IV – Zulresso

- **Lactation Risk Summary** - Available data from a **lactation study in 12 women** indicate that brexanolone is transferred to breastmilk in nursing mothers. However, **the relative infant dose (RID) is low, 1% to 2% of the maternal weight-adjusted dosage**. Also, as **brexanolone has low oral bioavailability (<5%) in adults, infant exposure is expected to be low.** There were no reports of effects on milk production. There are **no data on the effects of brexanolone on a breastfed infant.**

Brexanolone IV – Zulresso

- **ABUSE - Brexanolone infusions over a one hour period were compared to oral alprazolam administration (1.5 mg and 3 mg). On positive subjective measures of "drug liking", "overall drug liking", "high" and "good drug effects", the 90 mcg/kg dosage produced scores that were similar to placebo.** Scores on these positive subjective measures for both dosages of brexanolone 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for brexanolone 270 mcg/kg dosage were similar to those produced by both doses of alprazolam.
- In this study, **3% of subjects administered brexanolone 90 mcg/kg and 13% administered 270 mcg/kg reported euphoric mood, compared to none administered placebo during the one-hour administration**

Brexanolone IV – Zulresso

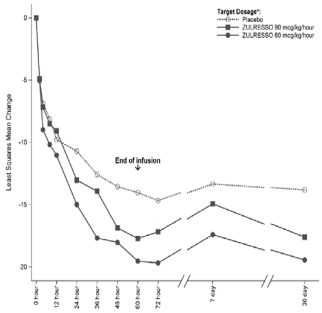
Table 3: Results for the Primary Endpoint – HAM-D Total Score (Studies 1 and 2)

Study Number	Treatment Group (# ITT subject)	Primary Endpoint: Change from Baseline in HAM-D Total Score at Hour 60		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI) Unadjusted p-value
1	ZULRESSO target dosage 90 mcg/kg/hour (n=41)*	28.4 (2.5)	-17.7 (1.2)	-3.7 (-6.9, -0.5) P=0.0252
	Placebo (n=43)	28.6 (2.5)	-14.0 (1.1)	
	ZULRESSO target dosage 60 mcg/kg/hour (n=38)*	29.0 (2.7)	-19.5 (1.2)	-5.5 (-8.8, -2.2) P=0.0013
	Placebo (n=43)	28.6 (2.5)	-14.0 (1.1)	
2	ZULRESSO target dosage 90 mcg/kg/hour (n=51)*	22.6 (1.6)	-14.6 (0.8)	-2.5 (-4.5, -0.5) P=0.0160
	Placebo (n=53)	22.7 (1.6)	-12.1 (0.8)	

HAM-D: Hamilton depression rating scale; ITT: intention to treat; SD: standard deviation; LS: least squares
SE: standard error; CI: confidence interval; *: statistically significant after multiplicity adjustments

Brexanolone IV – Zulresso

Figure 1: Change from Baseline in HAM-D Total Score Over Time (Days) in Study 1



Brexanolone IV – Zulresso

- **Sage said Zulresso will cost $34,000 without insurance, plus costs for staying in a hospital for about 3 extra days. ($7450.00/100 mg/20 mL vial)**
- **Sage expects availability by mid June.**
- **In the limited clinical trials brexanolone appeared to be more effective in more severe postpartum depressed patients, it worked within hours in most patients with about 75% of patients having at least a 50% reduction in symptoms at 60 hours and about 50% no longer being clinically depressed. 94% of patients did not relapse at 30 days but that is the limit of study duration.**

Brexanolone IV – Zulresso

- **Expect limited use of brexanolone. Look for it to be saved for severe postpartum depression.**
- There's **no evidence comparing it to other treatments...or for efficacy beyond one month.**
- Brexanolone is given as a one-time 60-hour infusion...**can cause sedation or loss of consciousness...and may have abuse or dependence risk.** This is why brexanolone **has a Risk Evaluation Mitigation Strategy (REMS) requiring administration and monitoring in a health care facility.**

New Black Box Warning for Febuxostat (Uloric)

- **.** [**2-21-2019**] The U.S. Food and Drug Administration (FDA) has concluded there is **an increased risk of death with febuxostat (Uloric) compared to another gout medicine, allopurinol**. This conclusion is based on our in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with febuxostat.
- **FDA is requiring a Black Box Warning and limiting the approved use of febuxostat to certain patients who are not treated effectively or experience severe side effects with allopurinol.**
- **Counsel patients to seek medical attention immediately if they experience chest pain, shortness of breath, rapid or irregular heartbeat, numbness or weakness on one side of the body, dizziness, trouble talking, or a sudden severe headache while taking febuxostat**

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout **(NEJM on-line 3-12-2018)**

- **6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). CARES Trial**
- In the modified intention-to-treat analysis, a **primary end-point (the first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization for unstable angina)** event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority).
- **All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death 1.34 [95% CI, 1.03 to 1.73]), febuxostat 134 cases (4.3%) vs. allopurinol 100 cases (3.2%) RRI 34%, ARI 1.1%, NNH 91.**

New Black Box Warning for Hypnotics

- [04-30-2019] The Food and Drug Administration (FDA) is advising that **rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths**. These behaviors appear to be more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than other prescription medicines used for sleep.

New Black Box Warning for Hypnotics

- Between December 16, 1992, and March 13, 2018. Of the **66 cases, 20 cases were reported as resulting in fatal outcomes. Forty-six cases reported serious non-fatal injuries; these patients usually did not remember experiencing these complex sleep behaviors.**
- **The adverse events included falls (n=22) with serious injuries such as intracranial hemorrhages, vertebral fractures, and hip fractures. Other events included self-injuries (n=7), fatal falls (n=6), accidental overdoses (n=5), hypothermia (n=5), suicide attempts (n=5), apparent completed suicides (n=4), fatal motor vehicle collisions (n=4), gunshot wounds (n=3), carbon monoxide poisoning (2), drowning or near drowning (n=2), burns (n=2), and homicide (n=1).**

Zolgensma – Onasemnogene abeparvovec-xioi by AveXis Inc/Novartis

- May 24, 2019 The FDA **Zolgensma (onasemnogene abeparvovec-xioi), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and a leading genetic cause of infant mortality.**
  - SMA is a **rare genetic disease caused by a mutation in the survival motor neuron 1 (SMN1) gene.** The gene encodes the survival motor neuron (SMN) protein – a protein found throughout the body, which is **critical for the maintenance and function of specialized nerve cells, called motor neurons. Children with this condition have problems holding their head up, swallowing and breathing**. These symptoms may be present at birth or may present by the age of 6 months. "Children with SMA experience difficulty performing essential functions of life. **Most children with this disease do not survive past early childhood due to respiratory failure"**

Zolgensma – Onasemnogene abeparvovec-xioi

- **Zolgensma is indicated for the treatment of children less than two years of age with SMA.** The product is **an adeno-associated virus vector-based gene therapy that targets the cause of SMA. The vector delivers a fully functional copy of human SMN gene into the target motor neuron cells. A one-time intravenous administration of Zolgensma results in expression of the SMN protein in a child's motor neurons, which improves muscle movement and function, and survival of a child with SMA.** Dosing is determined based on the weight of the patient.
- The primary evidence of effectiveness is based on results from the 21 patients treated with Zolgensma in the ongoing clinical trial. In this trial, there are 19 remaining patients, who range in age from 9.4 to 18.5 months; 13 of these 19 patients are at least 14 months of age. Compared to the natural history of patients with infantile-onset SMA, patients treated with Zolgensma also demonstrated **significant improvement in their ability to reach developmental motor milestones (e.g., head control and the ability to sit without support**).

Zolgensma – Onasemnogene abeparvovec-xioi

- The **most common side effects of Zolgensma are elevated liver enzymes and vomiting. Zolgensma has a boxed warning that acute serious liver injury can occur.** Patients with pre existing liver impairment may be at higher risk of experiencing serious liver injury. Clinical examination and laboratory tests to assess liver function should be completed prior to treatment with Zolgensma, and **patients' liver function should be monitored for at least three months after Zolgensma administration.**
- **The FDA granted this application Fast Track, Breakthrough Therapy, and Priority Review designations. Zolgensma also received Orphan Drug designation, which provides incentives to encourage the development of drugs for rare diseases. The FDA also awarded the manufacturer a rare pediatric disease priority review voucher.**

Zolgensma – Onasemnogene abeparvovec-xioi

- Novartis has announced the cost will be $2,125,000.00 for the single dose and it may be paid for 5 years. ($425,000/yr x 5)
- It has been evaluated by the ICER (Institute for Clinical and Economic Review) with a recent update on 5/24/19 and they now believe that based upon a value of $100-150,000 per QALY that the value-based price benchmark would be between $1.2 and $2.1 million

SELF EVALUATION

Pharmacotherapy Update - Parts 1 & 2

1. Which statement about the HPV vaccine (Gardasi89l-9) is not correct?

a. The FDA has stated that "Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers."
b. The CDC recommends 11- to 12-year-olds receive 2 doses of human papillomavirus (HPV) vaccine at least 6 months apart rather than the previously recommended 3 doses.
c. The CDC recommends 3 doses of HPV vaccine (0, 1–2, 6 months) for immunocompromised people age 9 through 26 years.
d. The FDA has expanded the approved use of the vaccine to include women and men aged 27 through 55 years of age.

2. T/F - 2 doses of MMR (measles-mumps-rubella) vaccine are 97% effective at preventing measles; 1 dose is 93% effective. Protection lasts for life.

3. T/F - Dec 20, 2017 the FDA announced that asthma and COPD inhalers "delivering fixed-dose combinations of inhaled corticosteroid (ICS) and long-acting beta agonists (LABA) drugs will no longer be required to carry a boxed warning about the possibility of asthma-related death associated with their use."

4. Which of the following medications is not a generic equivalent of Advair Diskus (twice daily fluticasone propionate and salmeterol inhalation powder) and should not be substituted by the pharmacy without approval of the prescriber?

a. Fluticasone propionate and salmeterol inhalation powder – Wixela Inhub Inhaler by Mylan
b. Fluticasone propionate and salmeterol powder Diskus by Prasco Laboratories

c. Fluticasone propionate and salmeterol inhalation powder AirDuo RespiClick by Teva
d. None of the above, all can be substituted

5. Which statement concerning the new monoclonal antibodies for the prevention/treatment of migraine headaches is not correct?

a. Erenumab-aooe (Aimovig) is a monoclonal antibody against the CGRP receptor and comes as a once monthly autoinjector.
b. Fremanezumab-vfrm (Ajovy) is a monoclonal antibody against the CGRP ligand and it comes as a prefilled syringe and can be dosed either monthly or quarterly.
c. Galcanezumab-gnlm (Emgality) is a monoclonal antibody against the CGRP receptor and is dosed 240 mg once a month with an autoinjector.
d. None of the above, all are correct

6. T/F - Cannabidiol Oral Solution – Epidiolex C-V controlled substance is FDA approved for the treatment of two rare pediatric seizure disorders Lennox-Gastaut syndrome and Dravet syndrome.

7. Which statement concerning Esketamine Nasal Spray (Spravato) is not correct?

a. Esketamine nasal spray is a C-III controlled substance approved for concurrent administration with an antidepressant medication for patients with severe treatment resistant depression.
b. Esketamine must be administered under the direct observation of a healthcare provider in healthcare setting certified in the program.
c. Patients must be monitored by a healthcare provider for at least 2 hours after administration of esketamine because of significant adverse effect potential.
d. Esketamine can be discontinued after 8 weeks with low risk of relapse

8. T/F - Brexanolone IV – Zulresso is the first FDA approved medication for post-partum depression administered as a 60 hour IV infusion with a healthcare provider available on site to continuously monitor the patient for excessive sedation and hypoxia.

9. T/F - The FDA has mandated a Black Box Warning for Febuxostat (Uloric) limiting the approved use of febuxostat to certain patients who are not treated effectively or experience severe side effects with allopurinol, based upon data from the CARES Trial which found an increase in CV and all-cause mortality with febuxostat vs. allopurinol.

10. T/F - The FDA has approved a new viral-vector gene therapy Zolgensma – Onasemnogene abeparvovec-xioi for children age 6 years and older with a rare genetic disease spinal muscular atrophy (SMA) at a cost of more than $2 million for the single IV dose.

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

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Understanding and Dealing with Personality Disordered Individuals – Parts 1 & 2

Many people may have certain defects of character. Recent studies in the behavioral sciences estimate that as many as one in five individuals is personality-disordered. A personality disorder is a syndrome of both character-based and biogenetic abnormalities that often goes undiagnosed and untreated. Personality-disordered individuals are profoundly flawed in that they have ingrained, recurring destructive patterns of thinking, feeling and behaving that create unnecessary disharmony, distress and even danger for themselves and for other people.

To the uninformed observer, character-flawed and personality-disordered individuals can appear normal, even "super-normal." They are typically intelligent, educated and gainfully-employed. Many are physically attractive, well-groomed, articulate and socially skilled. It is not unusual for high-functioning personality-disordered individuals to have truly exceptional abilities, talents and other socially-desirable qualities that set them apart from the ordinary. They can establish and sustain relationships and can hold a vast variety of positions of responsibility and importance. However, character-flawed and personality-disordered persons invariably sabotage their relationships and fail to meet their responsibilities consistently. These failures are costly to themselves and others, both financially and emotionally. Severely personality-disordered individuals rarely develop insight into their destructive patterns. Relatedly, they have a truly uncanny ability to project blame onto others for the problems they themselves create. Many will evidence little or no empathy for the distress and despair that they can cause others. When confronted with their toxic behavior, the personality-disordered person will often react defensively and then later withdraw or retaliate in an aggressive or passive-aggressive fashion.

In this highly pragmatic program, participants will learn both fundamental and advanced strategies for quickly recognizing and dealing strategically with individuals with character flaws and disorders of personality. Specifically, participants will learn:

1. How to differentiate between a character flaw and a disorder of personality;

2. How to quickly assess the critical signs and symptoms of personality disorders in members of their family, friends and business associates;

3. How to observe key principles for managing relationships with character-flawed and personality-disordered individuals. These principles include:

    a. Character-flawed and personality-disordered individuals should be treated with respect, kindness and compassion.
    b. You must be realistic about the potential danger and destructiveness of these individuals. This will involve setting and enforcing clear, reasonable boundaries and following through with appropriate consequences when these boundaries are challenged or violated.
    c. Understand that your persistent difficulties and problems with another individual are often a by-product of their character/personality pathology.
    d. You were likely drawn to the flawed person in part because of their attractive qualities, positive attributes and substantive achievements. This paradox may explain your wildly-conflicted feelings about this person and your reluctance to detach from them.
    e. Most individuals with disorders of character or personality will not accept the fact that they are mentally ill, will refuse treatment, and therefore will never change.
    f. Competent and compassionate mental health treatment can be helpful to anyone being held emotional hostage by a disordered individual.

4. How to implement specific strategies for navigating especially destructive relationships when avoiding the flawed individual is not an option, e.g., they are your boss or supervisor. These strategies include:

    a. Managing difficult conversations through active, empathic listening and conflict resolution techniques;
    b. Understanding and addressing cognitive distortions;
    c. Practicing mindful-based stress reduction;
    d. Focusing on where you have control and letting go of what is beyond your control; and
    e. Knowing when it is time to disengage completely.

5. How to detox from a pathological, stressful or otherwise toxic relationship and how to avoid these relationships in the future.

In the program, case history data from Dr. Shannon's 40 years of clinical practice along with film clips from motion pictures will be used to elucidate personality and character pathology. Participants will also have the opportunity to assess the likelihood that they are currently in a relationship with a character-flawed or personality-disordered individual.

I. What are personality flaws?

A. "(They) are brain-based dysfunctions of thinking and impulse control that lead to persistent patterns of personality and behavior that betray trust and destroy relationships." (Yudofsky, 2005).

B. A pathological pattern (in place by adolescence) of thinking, feeling and behaving that creates pain and distress for self and others. This problematic pattern can be a function of numerous factors including temperament, character, culture, religious and political beliefs, brain chemistry and poor nutrition. (Shannon, 2018).

1. Temperament (Traits)
   a. Harm avoidance (timidity vs. risk-taking)
   b. Novelty seeking (passivity vs. intrusiveness)
   c. Reward dependence (indifference vs. indulgence)
   d. Persistence (apathy vs. fanaticism)
   e. Socialization (introverted vs. extraverted)
2. Character (Habits) (Cloninger and Svrakic, 2000)
   a. Self-directedness - Disciplined, responsible, purposeful, resourceful, self-accepting
   b. Cooperativeness - Empathic, kind, compassionate, helpful, principled
   c. Self-transcendence - Idealistic, spiritual, intuitive, imaginative, acquiescent

* Social and behavioral scientists view character as the person's ability to modulate basic drives and emotions such as aggression, hunger, greed and sexual pleasure.

II. What makes personality flaws dangerous? (Yudofsky, 2005)

Personality flaws are dangerous if one or more of the following is true:

A. The person with the flaw does not perceive that they have a problem.

B. The person with the flaw has no desire to change.

C. The nature of the flaw is such that it cannot be treated/cured/corrected.

D. The nature of the flaw is such that there is the probability of future physical harm occurring to you or to others.

E. The nature of the flaw is such that there is the probability of violations of the law by the individual with the flaw.

F. The nature of the flaw is such that there is the probability that the person with the flaw will involve you in the breaking of the law.

III. What is a "Personality Disorder"?

A. A persistent pattern of cognitive, emotional and behavioral impairment that is the result of both temperamental and characterological flaws.

B. Common properties: (Masterson, 1981; Millon, 1981; Beck, Freeman and Davis, 2003)
1. Adaptive inflexibility – rigid, lack insight
2. Vicious cycles – tendency to repeat destructive patterns
3. Tenuous stability – periods of stability punctuated by periods of dysfunction
4. Pathological problem-solving – "DRAMA"
5. Denial or indifference re: impact of behavior on others
6. Disorder is ego-syntonic – They see themselves as normal.
7. Tendency to project blame/abdicate responsibility
8. Strong transference/countertransference – They project unresolved issues from past onto their relationship with you; they know how to "push your buttons."

C. Most significantly flawed personality types:
1. Paranoid (1 to 2%)
2. Schizotypal (1 to 2%)
3. Anti-social/Sociopathic (4%)

4. Borderline (4 to 6%)
5. Histrionic (2%)
6. Narcissistic (6 to 8%)
7. Compulsive/Perfectionistic (2%)

IV. What Causes Personality Flaws and Disorders?

A. Atypical brain chemistry (refer to Appendix A)
   1. Inherited?
   2. The result of physical, emotional, sexual trauma?

B. Developmental fixation, i.e., arrested development

C. Poor learning experiences i.e., parents may have been poor role models

D. Skill deficits resulting from life experience.

E. Maladaptive beliefs or "schema" that are largely learned. (refer to Appendix E)

F. Impact of culture, social class, religion, "political" climate

G. Impact of one's generational identify, e.g., "baby-boomers"

H. Impact of gender, gender-role and gender socialization

V. Personality Disorders At A Glance…

A. Paranoid (1 to 2%)
   1. They are unduly suspicious of the motives, intentions and behavior of others; they are distrustful.
   2. They take everything personally; humorless; non-disclosing.
   3. They believe they are being treated unfairly; they will complain that they are being oppressed and feel they are objects of hostility.
   4. They have gross disdain for persons who seem weak, soft, defective or emotionally vulnerable.
   5. They fault-find, are highly critical.
   6. They rarely get along with co-workers.
   7. They project blame onto external causes and people.
   8. If not in charge, they sabotage or flee.
   9. They fear yet invite the dislike of others.
   10. They have the highest incidence of domestic violence as perpetrators.
   11. They are highly susceptible to alcohol abuse and dependency.
   12. They have an extremely high rate of psychosomatic illness, esp. GI problems.
   13. They are prone to extreme, fanatical religious/political beliefs.
   14. They rarely seek treatment; often court-ordered into treatment and have questionable motivation at best.

B. Schizotypal (1 to 2%)
   1. They can appear schizophrenic-like, but they do not respond to anti-psychotic medications.
   2. They will drift from one endeavor to another with low investment/enthusiasm.
   3. They will appear odd, eccentric in behavior and appearance; will often have major hygiene problems, e.g., terrible body odor.
   4. They are often agitated, irritable and can be aggressive with little or no provocation.
   5. They will experience acute discomfort with close relationships; especially uncomfortable with displays of affection.
   6. You will never get a "thank you" in response to an act of kindness/consideration.
   7. They can be highly intelligent but will evidence little or no "common sense".
   8. They have a terrible prognosis for recovery.

C. Anti-social/Sociopathic (4%; men outnumber women 4:1)
   1. They display a pattern of disregard for, and violation of the rights of others.
   2. They are typically pathological liars; they come to believe their lies and distortions and will easily "pass" a lie-detector test.
   3. They have great difficulty sustaining employment and are typically overtly hostile to people in positions of authority.
   4. They do not abide by social rules and laws; "Rules are for fools – I don't let anybody tell me how to live my life…".
   5. They have deep financial difficulties largely because:
      a. They can't keep a job.
      b. They are highly impulsive/reckless with their money.
      c. They may engage in criminal behavior resulting in a wildly-fluctuating income.

d. They may spend much of their lives in and out of jail/prison.
e. They have a voracious appetite for stimulation, e.g., gambling, sex with prostitutes, drug/alcohol abuse, etc.
f. They can have expensive bills for legal representation.

6. They are callous and show little or no remorse for the pain that they cause others.
7. They lower their anxiety/insecurity by raising yours.
8. They attack in anticipation of being attacked; they are hyper-vigilant.
9. They have a great need to impress others.
10. They are sexually aggressive.
11. They achieve pleasure in the misfortune of others.
12. They are con-artists; they view others as vulnerable and will likely take advantage of them.
13. They have zero insight and tend to blame others for all of their difficulties.
14. They have the highest incidence of substance abuse of any psychiatric diagnosis; they start abusing drugs as teens or younger; they tend to be poly-substance abusers.
15. Terrible prognosis for recovery.

D. Borderline (4 to 6%; women outnumber men 4:1)
1. They straddle the "border" between sanity and madness.
2. Psychotic thinking and behavior is triggered by interpersonal stress, especially real or perceived abandonment.
3. They have profound feelings of emptiness and boredom which can alternate with hypo-manic-like feelings of excitation, agitation, irritability or euphoria.
4. They have boundless rage, which is either introjected (e.g., self-harm) or acted-out aggressively towards others.
5. They are highly manipulative, most especially when they sense you are distancing from them.
6. They hold their families hostage with outbursts of rage and suicidal threats.
7. They see themselves as victims or martyrs who need to be pitied or rescued.
8. They do not know how to differentiate between their projections and reality; are known for distorting the truth and making false accusations.
9. They crave intimacy but ultimately repel it, e.g., making unreasonable demands of a loved one.
10. They have a long history of toxic, unstable personal relationships.
11. They elicit the strongest countertransference reactions from professional caregivers.
12. They are prone to addictive disorders, self-mutilation, excessive body piercings and tattoos and somatic complaints, most especially auto-immune disorders such as fibro-myalgia.
13. Sixty-five percent have a history of sexual abuse.
14. Dialectical Behavioral Therapy is recommended; excellent prognosis for remission of most symptoms – 88% success rate.

E. Histrionic (2%)
1. They have an insatiable need for attention. This may manifest via constant demands for praise and re-assurance.
2. They use sexual seductiveness to gain praise or to manipulate others.
3. They have rapidly changing albeit shallow moods; they may appear "bipolar" in that their moods can change quickly and with little or no provocation.
4. They live in a perpetual state of denial and tend to avoid responsibility.
5. They can be extremely quick-witted, funny, and imaginative. These qualities, combined with a carefully-crafted youthful appearance, can make them very attractive to others.
6. They are easily bored with their spouses and partners; they tend to be flirtatious and will likely have multiple extra-marital affairs.
7. They prefer to be with partners who are detached/unemotional. They initially perceive these qualities as "emotional stability." Over time they perceive their partners as insensitive, disinterested or unappreciative.
8. They are phobic of aging and will go to great lengths and great expense to look significantly younger than their chronological age. Their personality deteriorates as they age.
9. As they get older, they will be especially prone to developing Somatoform and other psychosomatic disorders. They will use these psychogenic disorders to elicit special attention/empathy from their families and their medical providers.
10. Their primary goal is always affection and attention for themselves. They are rarely, if ever, concerned about the needs of others.
11. They frequently are "loud talkers" so that all will hear them.
12. Psycho-dynamic therapy is recommended with an uncertain prognosis.

F. Narcissistic (6-8%; males dominate at a ratio of 4:1)
1. They can initially appear "normal," even "super-normal."
2. They are morbidly self-absorbed and are typically self-centered and selfish.

3. They have an appalling lack of empathy and compassion for others but will expect extraordinary empathy and compassion from those close to them.
4. They have a sense of grandiosity which results in a profound and pervasive sense of entitlement. They are "special" and, as such, they are always entitled to special treatment. In addition, they should not be expected to play by the rules because they are so "special".
5. Their greatest fear is to be embarrassed or shamed. They tend to perceive any negative feedback as an assault/attack and will retaliate in a vengeful fashion. They never forget or forgive…
6. Relatedly, they fear being exposed as a fraud or failure. Many will exaggerate their accomplishments, educational background, work history and other achievements in order to sustain a grandiose public persona. They are seldom contented to be accepted by others. They want to be envied by others.
7. They are always seeking "the perfect mirror," i.e., the person who will reflect back all of the wonderful attributes the narcissist believes he possesses, e.g., "You're the greatest negotiator/deal maker…" But the "mirror" must never reflect the narcissist's imperfections, faults, or short-comings.
8. Many have serious problems with impulse control and judgement. They bore easily and will often create unnecessary drama/trauma just to assuage their boredom.
9. They rarely, if ever, take responsibility for their mistakes. They typically project blame onto others. If they are your boss or supervisor, they will take credit for your success and blame you for their failures.
10. They are rarely faithful to their domestic partners; they are oftentimes compulsively married and divorced; while married, they will typically have numerous sexual dalliances and affairs.
11. They are prone to addictive disorders, especially alcoholism, workaholism and sexual addictions.
12. They are pathologically self-reflective ("What could be more interesting to contemplate than me?") but have an astonishing lack of true insight. This dooms them to make the same terrible mistakes repeatedly.
13. They have a very poor prognosis if they enter psychotherapy after the age of 40. Insight-oriented, supportive psychotherapy will often time fuel pathological narcissism.
14. Sub-type: The Malignant Narcissist
    a. Paranoia, i.e., unduly suspicious of others.
    b. Prominent anti-social/sociopathic traits.
    c. Sadistic tendencies, i.e., will derive intense pleasure from causing pain, conflict or turmoil for others; will also have a mean-spirited, cruel sense of humor.
    d. No known treatment for this form of narcissism.

G. Compulsive-Perfectionistic (1-2%; males have a slight edge…)
1. They are typically preoccupied with excessive orderliness, perfectionism and mental and interpersonal "control"; their obsession with rules and details may undermine speed and efficiency at work.
2. They come across as aloof, cold, critical and joyless. They will not communicate feelings and will see others who do so as weak and inferior.
3. Their life is one endless "checklist." Many are workaholics and they typically equate their self-worth with doing rather than being.
4. They have the greatest level of occupational stress because they are tireless and fiercely dedicated to their job. As a result, their health and personal relationships both suffer.
5. They are terrible managers/leaders/supervisors:
    a. They will not delegate; this would result in loss of control;
    b. They will micromanage every task they must assign to others;
    c. They have un-godly, unrealistic expectations that few could meet much less exceed;
    d. They have impoverished social skills and won't be able to blend in with the group; and
    e. They are typically perceived as overbearing, controlling, neurotic and highly-critical; they are hypersensitive to negative feedback and are quick to interpret it as a put-down or insult.
6. They are very prone to depressive, anxiety-based and eating disorders. They have an unusually high incidence of alcohol abuse/dependency (60%).
7. Their moral/ethical/religious beliefs are extremely rigid and they are perceived as judgmental.
8. They tend to be miserly/stingy, bull-headed, willful, uncreative and inflexible; they also tend to be covertly hostile toward authority figures.
9. As parents, they have no concept of "unconditional love." Love is given or withheld based on the child's submitting exactly to the parent's way of doing things.
10. The recommended treatment includes:
    a. Targeted pharmacotherapy, e.g., use of anti-depressants
    b. Stress-management training

c. Training in mindfulness/meditation
d. Cognitive-behavioral psychotherapy
e. Prognosis: excellent with treatment

VI. Key Principles for Managing Flawed Relationships (Yudofsky, 2005)

A. Dealing with flawed individuals can be difficult, challenging, frustrating, and sometimes destructive. Never-the-less, people with these conditions should be treated with civility, respect and compassion.

B. You must adapt your behavior and alter your expectations of the flawed individual based on the reality of who they are, not who you think they could or should be. With most significantly flawed individuals, you will need to set and consistently enforce clear boundaries. If boundaries are violated, you will need to follow through with reasonable consequences.

C. If you are having a serious relationship problem, you are likely in a relationship with a person who has a significant character flaw or a full-blown personality-disorder. You may also have significant character or personality flaws. To address the relationship problem, start by focusing on your contribution to the problem.

D. You were likely attracted to the flawed person because of their attractive, substantive qualities. Your reluctance to leave the relationship may be due, in part, to this fact.

E. Character and personality-disordered individuals are excessively self-focused and self-involved. This makes these individuals reluctant (at best) to try to understand and accept other people's points of view. Relatedly, these individuals are typically oblivious to the effects of their behavior on those closest to them; or they simply don't care. There may also be tendencies to manipulate, exploit or otherwise take advantage of others, including close friends, colleagues and even family members.

F. Disorders of personality and character are complex, multifaceted phenomena. As such, they require a holistic, eclectic, multifaceted treatment approach to achieve even a small degree of remission. Treatment modalities may include:
1. Individual, strategic psychotherapy, e.g., cognitive-behavioral therapy, Dialectical Behavioral Therapy (DBT), etc.
2. Targeted pharmacotherapy, e.g., use of anti-seizure drugs to address problems with emotional stability and impulse control
3. Nutritional counseling, e.g., use of nutritional supplements to enhance production of serotonin to alleviate anxiety and depression
4. Substance-abuse counseling and 12-step programs, such as A.A., C.A., and N.A.
5. Marital/Family therapy, e.g., Family Systems Counseling
6. Neurofeedback to restore normal brain chemistry following severe trauma, e.g., E.M.D.R. to address P.T.S.D.
7. Training in meditation and mindfulness to optimize brain chemistry and enhance neurochemical resilience vis a vis stress.

G. Sadly, many (if not most) people with disorders of character and personality will not accept that they have problems. They will refuse or be non-compliant with treatment. They will not likely change. Relatedly, if you are in a relationship with a disordered individual, they will likely blame you for all of the problems that they themselves create. This is commonly called "gaslighting," named so after a famous motion picture ("Gaslight") wherein the central female character is brainwashed and abused by her psychopathic husband.

H. Competent and compassionate professional treatment can be very helpful to a person currently in or desiring to relinquish a toxic relationship with a disordered individual. The best treatment will help that person learn how to protect him/herself from the devaluations, distortions and exploitations that frequently occur in toxic relationships. In addition it will teach the individual how to compute a pro-vs-con "relationship calculus" culminating in a decision regarding their future participation in or detachment from the troubled relationship.

VII. Critical Principles for Recovery and Growth

A. While there are mental health treatments for disorders of character and personality, they remain largely incurable, untreatable and widespread. Moreover, the vast majority of significantly flawed individuals will never seek mental health treatment. Bottom line: Character- flawed and personality-disordered individuals are not likely going to change. What you see (and don't see) is what you get.

B. If complete detachment is not an option, you must develop critical skills for successfully navigating the dangerous waters of character and personality-pathology. These skills would include teaching yourself and others how to:
1. Quickly recognize the obvious and not-so-obvious signs and symptoms of a character/personality pathology, i.e., calling out toxic, manipulative behavior for what it really is vs. "normalizing" bad behavior when it is convenient to do so. E.g., "Sexual Harassment" vs. "Boys will be boys…"
2. Address and set limits with inappropriate behavior. This is no easy task, most especially if there is a power differential, e.g., the flawed individual is your boss or supervisor.
3. Adapt/tailor communication style to the flawed personality in question. There is no "one size fits all" approach when it

comes to dealing with toxic individuals. For example, it is generally not advisable to confront a narcissist or sociopath directly. This will likely precipitate an extreme, retaliatory, defensive response. A better approach would be to appeal to the individual's selfish self-interest. (Refer to Appendices B, C and D)

4. Resist the pull to be drawn into the various "psycho-dramas" of character-flawed and personality-disordered individuals. For example, the person with Borderline personality disorder is interested in seeing herself as a victim. She will work diligently to seduce you into being her next hero, i.e., the person who will rescue her from all of her misery and pain. In a similar fashion, the narcissistic individual will initially try to place you upon a pedestal provided that you always affirm his greatness and never challenge his toxic behaviors.

C. You must be committed to learning something positive and adaptive from your experience(s) with character-flawed and personality-disordered individuals. In other words, break the pattern, break the cycle before it breaks you. This process of learning and recovery will involve the following steps:
   1. Education for you and those you care about (see comments above).
   2. Validation – e.g., helping others through their dark experiences and showing them that they are not alone. Sharing your experiences with others and understanding how you and they were "conned", manipulated, betrayed or otherwise abused. Clarifying how you (and others) were "triggered", i.e., what was your piece of the toxic relationship?
   3. Healing/Transcendence – Here you shift the focus from the disordered individual to you. This may involve:
      a. Identifying and mourning losses;
      b. Clarifying what you may have gained from the toxic experience, e.g., wisdom;
      c. Developing healthy boundaries and enforcing them consistently;
      d. Identifying self-esteem defects that may have made you more vulnerable to victimization. Remedying these through cognitive-behavioral therapy; and
      e. Clarifying what healthy and unhealthy relationships look like.
   4. Freedom:
      a. You can clearly and quickly identify disordered individuals; the fog has lifted…
      b. You have no allusions about changing or transforming the disordered individual. Their condition is toxic and likely terminal.
      c. You recognize that nothing positive or of substance can be gained from interacting with this individual. If you must interact with this person, you will do so in a mindful, strategic and peaceful way.
      d. You will devote your energy to psychologically healthy, empathic, reciprocal individuals.
      e. You understand that you deserve to be with people who respect, love and care for you. Bottom line: surround yourself with safe, respectful and supportive people and offer them these same qualities.

VIII. Appendices

A. Primer on neuro-psychology of personality disorders
B. Five critical strategies for reasoning with individuals with disorders of character and personality
C. Specific listening skills for avoiding unnecessary conflict with disordered individuals
D. A model for having especially difficult conversations with disordered individuals
E. Cognitive distortions for personality disorders

IX. References

***Appendix A:**

Biological/Neurochemical View of Personality Flaws and Disorders

A. Personality-disordered patients have atypical brain chemistry.

B. The atypical brain chemistry may be the result of a biogenetic predisposition, pre-birth trauma, birth trauma, post-birth psychological or physical trauma, physical or emotional neglect, medical conditions or a combination of these factors

C. While many areas of the brain may be affected, the primary locus of the imbalance will be in the cerebral cortex, the prefrontal cortex and sections of the limbic system notably the amygdala and the hippocampus.
   1. Prefrontal cortex abnormalities will include:
      a. Impaired executive functions:
         (1.) Sociopathic manipulation alternating with:
         (2.) Lack of forethought/impulsivity in making another decision; and
         (3.) An unwillingness to change/alter one's course of action.

b. Impaired impulse control and emotional regulation:
   (1.) Inability to sense/respond appropriately to the emotions of others (e.g., empathy)
   (2.) Pathological risk-taking
   (3.) All forms of addiction
   (4.) Inability to delay gratification

D. Neurotransmitters, notably serotonin, dopamine and norepinephrine, will figure prominently in the chemical imbalance which underlies the personality pathology. These neurotransmitter excesses or deficits will have profound effects on the patient's mood, motivation, interpersonal behavior, impulse control and affect regulation/modulation.

E. Effective treatment will need to include a pharmacological intervention targeted to specific symptoms along with strategic psychotherapy and other treatment modalities.

* From: Carlen, M. (2017). What constitutes the prefrontal cortex? In: Science, (358). 478-481.

Appendix B:

Critical Pathways For Effective Reasoning

A. Assuring that the person feels heard.
   1. Active Empathic Listening
   2. Emotional healing begins when the patient's feelings, observations and concerns are validated by the healthcare provider.

B. Focus on feelings.
   1. What are the patient's emotional triggers/suppressors?
   2. What feelings get triggered, e.g., anger?
   3. What does the patient currently do to calm/soothe themselves once triggered?

C. Focus on beliefs/schema.
   1. What core beliefs are being triggered?
      → "I'm not good enough."
      → "I'm being abandoned."
      → "I'm entitled."
   2. What makes these beliefs so compelling?
      → Reinforced by parents/peers?
      → Maintain patient's identity?
   3. What can be done to challenge/change these beliefs?
      → Cognitive-behavioral psychotherapy?
      → Thought-stopping?
      → "Where's the evidence/data to support this belief?
      → "Can I change my narrative?"

D. Identify the patient's core strengths:
   1. Resilience
   2. Intrapersonal skills, e.g., self-soothing, distracting techniques
   3. Interpersonal skills, e.g., easily connects with others in a group such as AA or NA
   4. Emotion regulation skills:
      → deep breathing; use of imagery
      → counting slowly from 1 to 10
      → the ice-cube strategy
      → waiting 24 hours before expressing anger

E. Core emotional concerns:
   1. To feel understood
   2. To feel appreciated
   3. To be given the benefit of the doubt
   4. To be treated as an equal
   5. To be treated respectfully

6. To have the freedom to decide

F. Beyond reason:
   1. Rage
   2. Acute mania
   3. Delirium
   4. Substance-induced states
   5. Psychosis
   6. Dementia/Organic Brain Syndrome

Appendix C:

Active Empathic Listening Skills

1. Face the speaker.
2. Maintain eye contact.
3. Remain calm and relaxed:
   a. Breathing deeply
   b. Monitoring your voice
   c. Seeing the unreasonable individual as a "gift"
   d. Defensive behavior seen as a measure of pain
4. Be attentive.
5. Be open-minded and flexible.
6. Listen to the words for meaning.
7. Summarize/paraphrase what the person says.
8. Watch the person's body language for clues.
9. Be aware of your body language.
10. Refrain from interrupting.
11. Wait for the person to pause before speaking.
12. Ask open-ended, clarifying questions.
13. Do not judge the other person.
14. Try to understand what the person is feeling and validate that feeling.
15. Use statements like, "I understand how you feel."

From: Leutenberg, E.A. & Liptak, J. J. (2012). Coping with Difficult People Workbook.

Appendix D:

Model for Having Difficult Conversations

A. State your positive intent.
   1. Explain your purpose, highlighting the benefit to the other person.
   2. Helpful for intent to convey empathy or to affirm other person in some way.

B. Tell the truth fast.
   1. Get to the point quickly.
   2. Be factual and specific.
   3. Explain impact; i.e., negative consequences.

C. Listen and understand.
   1. Invite reactions and inquire.
   2. Listen intently; acknowledge the other person's feelings.
   3. Check your understanding.

D. Find common ground.
   → Summarize your shared interest or goal. e.g., "We both want…"

E. Identify options and your action plan.
   1. Identify possible courses of action and the pros and cons of each.
   2. Agree on your approach – a plan of action for both of you.

F. Express appreciation.
   1. Convey positive regard, i.e., thanks, admiration or appreciation. e.g., "This wasn't easy, and I appreciate your openness…"
   2. "How are you feeling about our conversation…?"

G. Trouble-shooting:
   1. Beforehand, adopt a positive mindset, or at least a neutral one. Do not come across as frustrated, angry or blaming. Be respectful and open.
   2. If the person resists:
      a. Empathize with resistance.
      b. Repeat steps "A" through "F" in the face of continuing resistance.
   3. If you're on the receiving end, open your mind.

Appendix E:

Cognitive Distortions for Personality Disorders

PARANOID PERSONALITY DISORDER

1. People will eventually try to hurt me.
2. People cannot be trusted. They will always take advantage of me.
3. People will try to bother or annoy me.
4. Don't get mad, get even.
5. Any insult, no matter how slight, directed at me should be punished.
6. Always be prepared for the worst.
7. To compromise is to surrender.
8. Avoid intimacy.
9. If I get close to people they can find out my weaknesses.
10. Keep alert for anyone who has power. They can hurt me.

SCHIZOTYPAL PERSONALITY DISORDER

1. Don't let people get too close.
2. People will try to engulf or control me.
3. Don't express affection or gratitude; others will take advantage of me if I do.
4. My perceptions are more reliable than those of others.
5. I am gifted with a special type of vision, psychic or otherwise.
6. I can't be bothered with trivialities, like paying my bills or daily hygiene.
7. I am more intelligent than most other people.

ANTISOCIAL PERSONALITY DISORDER

1. Rules are meant for others.
2. Only fools follow all of the rules.
3. Rules are meant to be broken.
4. Look out for Number 1.
5. My pleasure comes first.
6. If others are hurt, offended, or inconvenienced by my behavior, that is their problem.
7. Do it now!
8. I will not allow myself to be frustrated.
9. I will do whatever I must to get whatever I want.
10. I am really smarter than most everybody else.

BORDERLINE PERSONALITY DISORDER

1. I am not sure who I am.
2. I will eventually be abandoned.
3. My (psychic) pain is so intense that I cannot bear it.
4. My anger controls me. I am incapable of modulating my behavior.
5. My feelings control me. I cannot modulate my feelings.
6. S/he is so very, very good that I am so lucky.
7. S/he is so very, very awful that I cannot bear them.
8. When I am overwhelmed I must escape (by flight or suicide).

HISTRIONIC PERSONALITY DISORDER

1. Appearances are important
2. People are judged on external appearance.
3. I must be noticed.
4. I must never be frustrated in life.
5. I must get everything I think that I want.
6. Emotions should be expressed quickly and directly.
7. Beauty is the most important consideration in judging someone.

NARCISSISTIC PERSONALITY DISORDER

1. I must have my way in every interaction.
2. I must not be, in any way, foiled in seeking pleasure or status.
3. I am more special than anyone else.
4. I should only have to relate to people like me.
5. I must be admired.
6. No one should have more of anything that I have.

COMPULSIVE-PERFECTIONISTIC PERSONALITY DISORDER

1. There are strict rules in life.
2. By focusing on the details of a situation, one will reduce the chances of making errors.
3. A person is defined by what they do.
4. The better the job you do the better person you are.
5. Rules must be adhered to without alteration.
6. Never discard anything that may be of some value.
7. Emotions must be controlled.

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Online Resources
www.greatergood.berkeley.edu: Fabulous site for research, education, and practices related to "the science of a meaningful life"
www.mindful.org: Wonderful practices for nurturing well-being: for example *10 mindful attitudes that decrease anxiety…the 3-minute breathing space practice*
www.thework.com: Byron Katie's approach to "identifying and questioning the thoughts that cause all the anger, fear, depression, addiction and violence in the world."

SELF EVALUATION

Understanding and Dealing with Personality Disordered Individuals – Parts 1 & 2

1. A personality flaw is:

- a. Sometimes a habit-based, maladaptive way of thinking or behaving.
- b. Sometimes the result of a neurochemical abnormality that is either inherited or acquired from trauma.
- c. Never treatable/correctable.
- d. A and B are true.

2. Which of the following is a personality trait?

- a. Harm avoidance (timidity vs. risk-taking)
- b. Self-directedness
- c. Cooperativeness
- d. Self-transcendence

3. Which of the following is a personality habit?

- a. Novelty-seeking behavior
- b. Reward dependence
- c. Cooperativeness
- d. Socialization

4. Personality or character flaws are dangerous when:

- a. The person with the flaw does not perceive themselves as having a problem.
- b. The person with the flaw projects blame onto others for the flaw.
- c. The nature of the flaw is such that it cannot be treated or changed.
- d. All of the above are true.

SELF EVALUATION

Understanding and Dealing with Personality Disordered Individuals – Parts 1 & 2 cont.

5. Which of the following is not a common property of personality- disordered individuals?

a. All are untreatable/incurable.
b. Adaptive inflexibility
c. Tenuous stability
d. Pathological problem-solving

6. Which of the following is not a symptom of paranoid personality-disorder?

a. They are unduly suspicious of the intentions and behavior of others.
b. They paradoxically have a light-hearted, delightful sense of humor.
c. They have the highest incidence of perpetrating domestic violence.
d. They tend to be fault-finding and highly critical.

7. Schizotypal individuals:

a. Can appear to have schizophrenic tendencies but do not respond well to anti-psychotic medications.
b. Are often agitated, irritable and anxious, most especially in social situations.
c. Are generally uncomfortable with displays of affection.
d. All of the above are true.

8. Anti-social (sociopathic) individuals:

a. Have a profound sense of identity confusion.
b. Are pathologically obsessed with rules and details and often fail to grasp the “bigger picture.”
c. Are pervasively dishonest and disloyal.
d. Tend to avoid social interaction.

9. Which of the following statements is true?

a. Setting and enforcing clear, consistent boundaries is critical when dealing with flawed or personality-disordered individuals.
b. You may need to alter your expectations and adapt your communication style when dealing with flawed/disordered individuals.
c. Personality-disordered individuals invariably attract and develop relationships with other personality-disordered individuals.
d. All of the above are true.
e. Only A and B are true.

10. Which of the following is a critical principal for recovering from a toxic relationship?

a. If possible, detach completely from the toxic individual.
b. If detaching is not an option, you will need to develop critical skills, such as setting boundaries and enforcing consequences with the toxic person.
c. You must resist the pull to be drawn into the “psycho-drama” of the toxic individual’s life, e.g., resist the desire to “rescue the victim.”
d. You must be committed to learning something positive/adaptive from your stressful experience with the toxic individual.
e. All of the above are critical principals.

Answer Key: 1. D, 2. A, 3. C, 4. D, 5. A, 6. B, 7. D, 8. C, 9. E, 10. E

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Dr. Clauw is a consultant for Abbott Pharmaceutical, Aptinyx, Astellas Pharmaceutical, Cerephex, Daiichi Sankyo, Pfizer Inc., Samumed, Theravance, Tonix and Zynerba.

You may contact Dr. Clauw with any questions or comments at (764) 998-6939 or dclauw@umich.edu.

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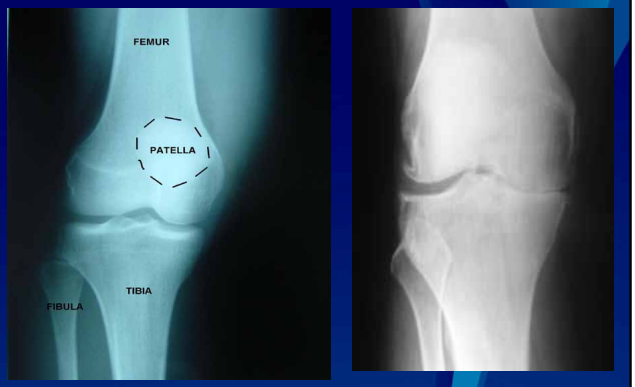
University of Michigan
Professor, Anesthesiology, Medicine & Psychiatry

Chronic Pain Diagnosis and Treatment: Understanding the Underlying Mechanisms

Which person has pain?



Osteoarthritis of the knee - I

- Classic "peripheral" pain syndrome
- Poor relationship between structural abnormalities and symptoms[1]. In population-based studies:
  - 30 – 40% of individuals who have grade 3/4 K/L radiographic OA have no symptoms
  - 10% of individuals with severe pain have normal radiographs
- Psychological factors explain very little of the variance between symptoms and structure[2]
- We sometimes delude ourselves into thinking that our current therapies are adequate
  - NSAIDs, acetaminophen, and even opioids have small effect sizes[3,4]
  - Arthroplasty does not predictably relieve pain

(1) Creamer P, et. al. Br J Rheumatol 1997; 36(7):726-8. (2) Creamer P, et. al. Arthritis Care Res 1998; 11(1):60-5. (3) Bjordal JM, et. al. Eur J Pain 2007; 11(2):125-38. (4) Zhang W, et. al. Ann Rheum Dis 2004; 63(8):901-7.

Evolution of Thinking Regarding Fibromyalgia

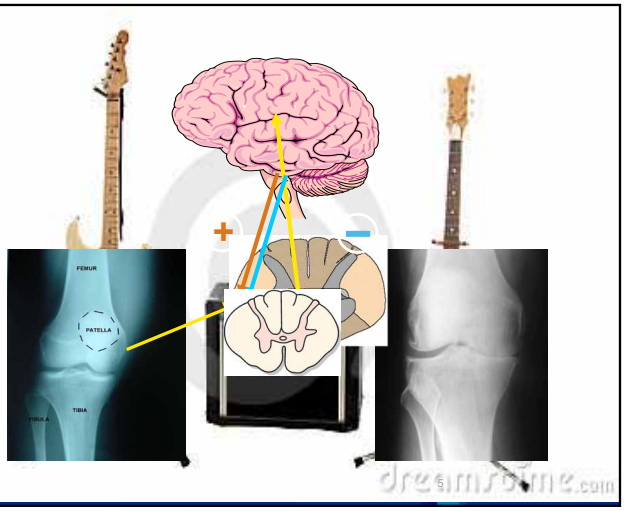
American College of Rheumatology (ACR) Criteria

- Discrete illness
- Focal areas of tenderness
- Pathophysiology poorly understood and thought to be psychological in nature

- Final common pathway (i.e. pain centralization)
- Part of a much larger continuum
- Not just pain
- Pathophysiology fairly well understood and is a CNS process that is independent from classic psychological factors

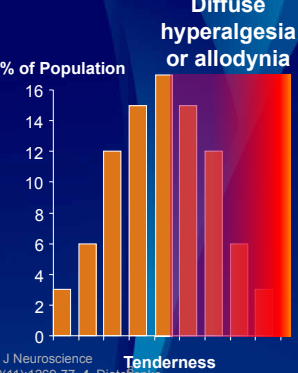
Mechanistic Characterization of Pain
Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Centralized
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
Screening tools		PainDETECT	Body map or FM Survey
Treatment	NSAIDs, injections, surgery, ? opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, non-pharmacological therapies
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain



Pain and sensory sensitivity in the population

- Like most other physiological processes, we have a "volume control" setting for how our brain and spinal cord processes pain[1]
- This is likely *set* by the genes that we are born with[2-4], and *modified* by neurohormonal factors and neural plasticity
- The higher the volume control setting, the more pain we will experience, irrespective of peripheral nociceptive input



1. Mogil JS. PNAS, 1999;96(14):7744-51. 2. Amaya et. al. J Neuroscience 2006;26(50):12852-60. 3. Tegeder et.al., NatMed. 2006;12(11):1269-77. 4. Diatchenko et. al. HumMolGenet. 2005;14(1):135-43.

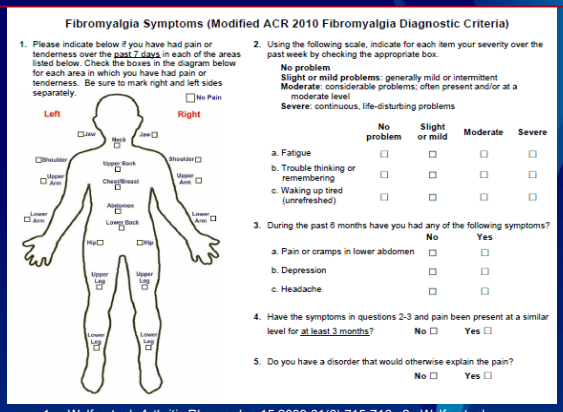
Fibromyalgia-ness

- Term coined by Wolfe to indicate that the symptoms of FM occur as a continuum in the population rather than being present or absent [1]
- In rheumatic disorders such as osteoarthritis, rheumatoid arthritis, lupus, low back pain, etc. this score is more predictive of pain levels and disability than more objective measures of disease [2,3]
- Domain overlaps with somatization in many regards, and there are many questionnaires that collect somatic symptom counts as a surrogate for this construct

1.Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al. 2.*J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

7

Concept of "Fibromyalgia-ness"



1. Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al.
2. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

Sub-threshold FM is Highly Predictive of Surgery and Opioid Non-responsiveness in Patients Undergoing Arthroplasty and Hysterectomy

- Primary hypothesis of studies is the measures of centralized pain in OA (FMness) will predict failure to respond to arthroplasty and hysterectomy
- Extensive preoperative phenotype using validated self-report measures of pain, mood, and function
- Two outcomes of interest:
  - Postoperative opioid consumption
  - Pain relief from procedure at 6 months

1. Brummett, C.M., et al., Anesthesiology, 2013. **119**(6): p. 1434-43.
2. Brummett, C.M., et al., Arthritis Rheumatol, 2015. 67(5):1386-94.
3. Janda, A.M., et al., Anesthesiology, 2015. **122**(5): p. 1103-11.

Variables Analyzed

- Age
- Sex
- Surgery (Knee vs Hip)
- Primary anesthetic (GA vs neuraxial)
- Home opioids (IVME)
- Pain severity (BPI)
  - Overall
  - Surgical site
- Neuropathic pain score (PainDETECT)
- Depression (HADS)
- Anxiety (HADS)
- Catastrophizing
- Physical function-WOMAC

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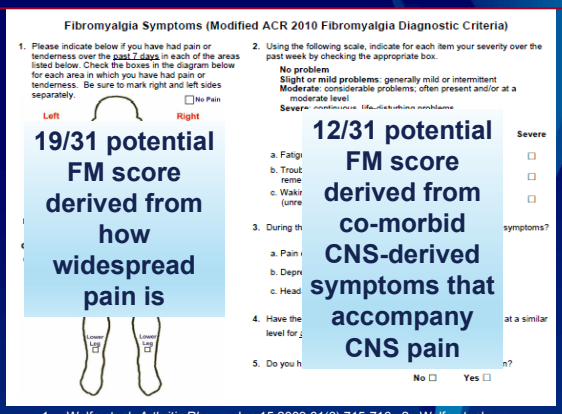
"Fibromyalgia-ness" can be scored 0-31

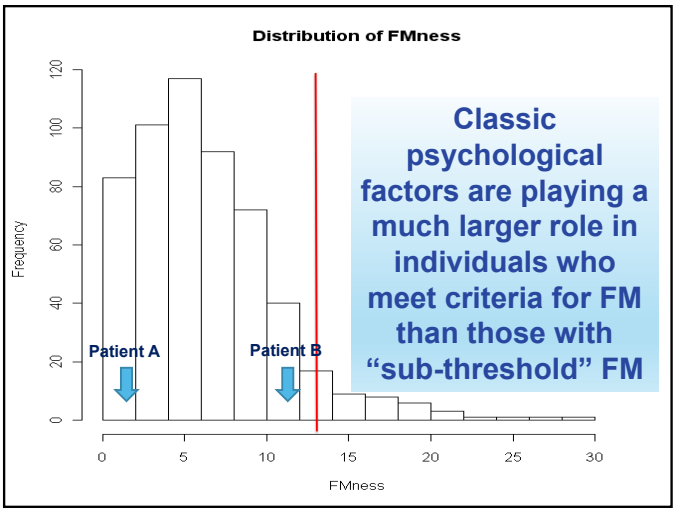


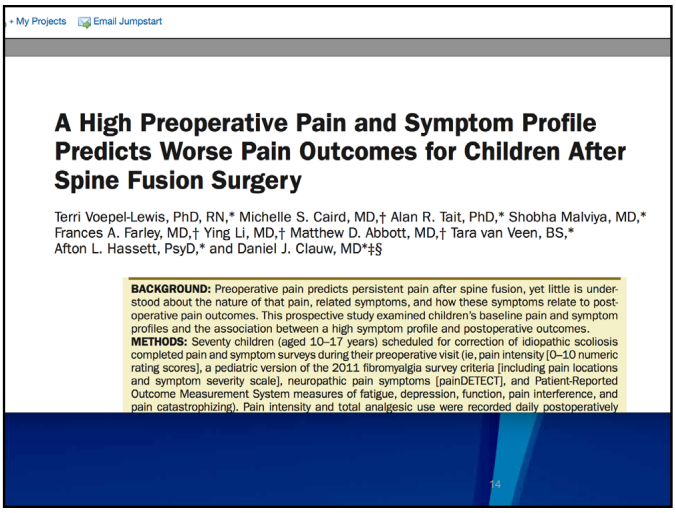
1. Wolfe et. al. *Arthritis Rheum.* Jun 15 2009;61(6):715-716. 2. Wolfe et. al.
2. *J Rheumatol.* Feb 1 2011. 3. Clauw DJ. JAMA, 2014.

Each one point increase in fibromyalgianess led to:

- 9 mg greater oral morphine requirements during acute hospitalization (8mg greater when all individuals taking opioids as outpatients excluded)
- 20 – 25% greater likelihood of failing to respond to knee or hip arthroplasty (judged by either 50% improvement in pain or much better or very much better on patient global)
- These phenomenon were linear across entire scale up to a score of approximately 18 - and equally strong after individuals who met criteria for FM were excluded
- This phenomenon was much stronger than and largely independent of classic psychological factors

12





The widespreadedness of pain (half of the 2011 FM criteria) predicts increased responsiveness to duloxetine in Low Back Pain

- In LBP, responsiveness to duloxetine was strongly related to number of sites on the Michigan Body Map.
  - Average number of sites of pain in this LBP study was 3 – 4
  - At 14 weeks, using any measure of pain improvement, individuals with more body sites of pain were significantly more likely to respond
  - Relative response rate for responders (30% improvement in pain)
    - MBM pain sites = 1 RR = **1.07**
    - MBM sites = 2 **1.30**
    - MBM sites = 3 **1.34**
    - MBM sites = 4 **1.47**
    - MBM sites > 5 **1.60**

1. Alev et. al. Clinical Journal of Pain, 2017

15

In RA, the residual pain and fatigue seen despite treatment with biologics can be treated as such

- In a large cohort of RA patients being treated at a US academic medical center, 47.3% continued to report having moderate to high levels of pain and fatigue. Most of these patients had minimal signs of inflammation but high levels of FM or Fmness.[1]
- Using quantitative sensory testing, active inflammation was associated with heightened pain sensitivity at joints (peripheral sensitization), whereas poor sleep was associated with diffuse pain sensitivity as noted in FM (central sensitization or centralized pain).[2]
- In a cross-over trial of six weeks of milnacipran in RA patients, in the overall group there was no statistical improvement, but in the subgroup with the least inflammation (swollen joint count </= 1) milnacipran decrease average pain intensity more than placebo (95% CI -2.26 to -0.01, p = 0.04).[3]

1. Lee YC, et. al. *Arthritis Res Ther.* 2009;11(5):R160. 2. Lee YC, et. al. *Arthritis & rheumatology.* 2014;66(8):2006-2014. 3. Lee YC, et. al. *J Rheumatol.* 2016;43(1):38-45.

16

Mechanistic Characterization of Pain

Variable degrees of any mechanism can contribute in any disease

	Nociceptive	Neuropathic	Centralized
Cause	Inflammation or damage	Nerve damage or entrapment	CNS or systemic problem
Clinical features	Pain is well localized, consistent effect of activity on pain	Follows distribution of peripheral nerves (i.e. dermatome or stocking/glove), episodic, lancinating, numbness, tingling	Pain is widespread and accompanied by fatigue, sleep, memory and/or mood difficulties as well as history of previous pain elsewhere in body
Screening tools		PainDETECT	Body map or FM Survey
Treatment	NSAIDs, injections, surgery, ? opioids	Local treatments aimed at nerve (surgery, injections, topical) or CNS-acting drugs	CNS-acting drugs, non-pharmacological therapies
Classic examples	Osteoarthritis Autoimmune disorders Cancer pain	Diabetic painful neuropathy Post-herpetic neuralgia Sciatica, carpal tunnel syndrome	Fibromyalgia Functional GI disorders Temporomandibular disorder Tension headache Interstitial cystitis, bladder pain

Mixed Pain States

Centralization Continuum

Proportion of individuals in chronic pain states that have centralized their pain

Peripheral — Centralized

Acute pain
Osteoarthritis
RA
SC disease
Ehler's Danlos
Low back pain
Fibromyalgia
Tension HA
TMJD
IBS

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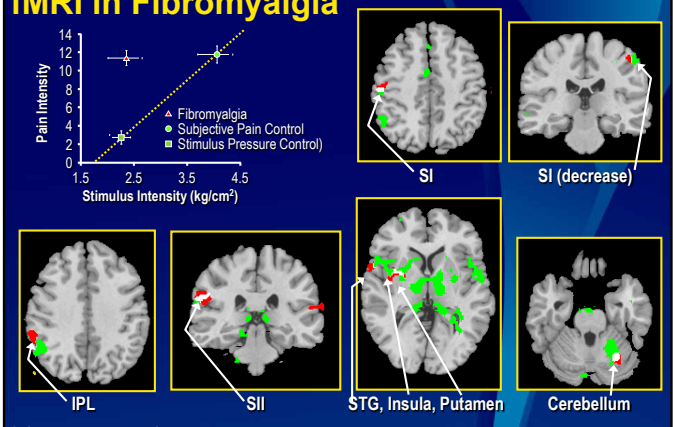
Pathophysiology of centralized pain states

- Most patients display augmented pain and sensory processing on quantitative sensory testing and functional neuroimaging[1,3]
- Manifest by increased connectivity to pro-nociceptive brain regions and decreased connectivity to anti-nociceptive regions[2,3]
- These abnormalities are being driven by imbalances in concentrations of CNS neurotransmitters that control sensory processing, sleep, alertness, affect, memory[3,4]
- Autonomic, HPA, and peripheral abnormalities likely play a prominent role in some individuals

1. Phillips, K. and D.J. Clauw. Arthritis Rheum, 2013. **65**(2): p. 291-302. 2. Napadow, V., et al., Arthritis Rheum, 2012. **64**(7): p. 2398-403. 3. Harris, R.E., et. al. Anesthesiology, 2013. **119**(6): p. 1453-1464. 4. Schmidt-Wilcke, T. and D.J. Clauw, Nature reviews. Rheumatology, 2011. **7**(9): p. 518-27.

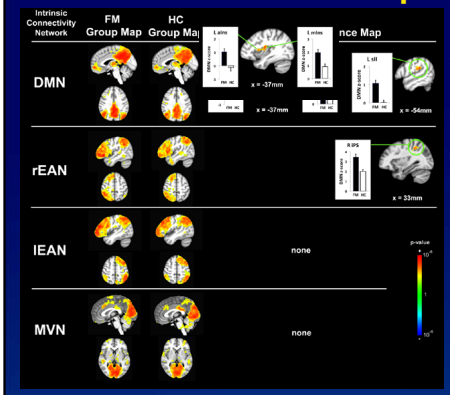
fMRI in Fibromyalgia



STG=superior temporal gyri; SI=primary somatosensory cortex
SII=secondary somatosensory cortex; IPL=inferior parietal lobule.

Gracely. *Arthritis Rheum.* 2002;46:1333-1343.

Intrinsic Brain Connectivity is Altered in FM patients



- **In FM, DMN and rEAN show greater intrinsic connectivity within component DMN (PCC), and rEAN (iPS) as well as limbic (insula), and sensorimotor (SII) regions outside conventional network boundaries.**
- **All FM vs. HC differences driven by greater connectivity for FM patients**

Napadow et al, *Arthritis Rheumatism* 2010

Changes in size and shape of brain regions indicate CNS neuroplasticity in chronic pain

- Apkarian[1] was first to show that chronic pain may be associated with decrease of size of brain areas involved in pain processing
- More recently seen in virtually all other chronic pain states including headache,[2] IBS,[3] FM[4]
- May be partially due to co-morbid mood disturbances[6]
- Data from NIH MAPP network presented at 2016 IASP (Kutch et. al.) suggests *increase* in size of and connectivity to S1 may represent neural signature for widespreadedness of pain

1. Apkarian et al. *J Neurosci.* 2004;24:10410-5. 2. Schmidt-Wilcke et al. *Pain.* 2007;132 Suppl 1:S109-16. 3. Davis et al. *Neurology.* 2008;70:153-4. 4. Kuchinad et al. *J Neurosci.* 2007;27:4004-7. 5. Chen et al. *Psychiatry Res.* 2006;146:65-72. 6. Hsu et. al. *Pain.* Jun 2009;143(3):262-267. 7. Kutch et. al. IASP 2016

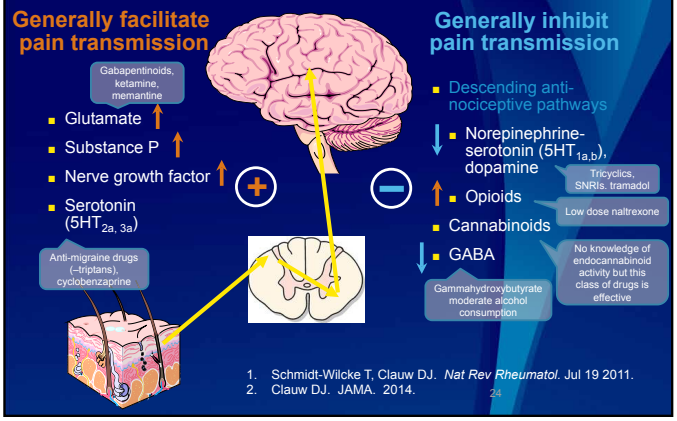
Pharmacological Therapies for Fibromyalgia (i.e. Centralized Pain)

Strong Evidence	▪ Dual reuptake inhibitors such as ▪ Tricyclic compounds (amitriptyline, cyclobenzaprine) ▪ SNRIs and NSRIs (milnacipran, duloxetine, venlafaxine?) ▪ Gabapentinoids (e.g., pregabalin, gabapentin)
Modest Evidence	▪ Tramadol ▪ Older less selective SSRIs ▪ Gamma hydroxybutyrate ▪ Low dose naltrexone ▪ Cannabinoids
Weak Evidence	▪ Growth hormone, 5-hydroxytryptamine, tropisetron, S-adenosyl-L-methionine (SAMe)
No Evidence	▪ Opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, benzodiazepine and nonbenzodiazepine hypnotics, guanifenesin

Modified from Clauw *JAMA.* 2014

CNS Neurotransmitters Influencing Pain

Arrows indicate direction in Fibromyalgia

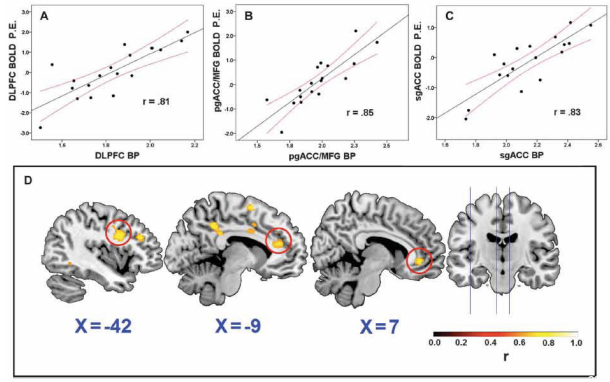


1. Schmidt-Wilcke T, Clauw DJ. *Nat Rev Rheumatol.* Jul 19 2011.
2. Clauw DJ. JAMA. 2014.

PAIN

Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study

Andrew Schrepf[a,*], Daniel E. Harper[a], Steven E. Harte[a], Heng Wang[a], Eric Ichesco[a], Johnson P. Hampson[a], Jon-Kar Zubieta[a], Daniel J. Clauw[a], Richard E. Harris[a]



Commentary

PAIN

Hijacking the endogenous opioid system to treat pain: who thought it would be so complicated?

Daniel Clauw

In this issue, there is an especially interesting and important special review by Ballantyne and Sullivan entitled, "The discovery of endogenous opioid systems: what it has meant for the clinician's understanding of pain and its treatment".[1] This review adds to these authors' significant prior contributions to the pain field, as they are now proposing that many of the problems associated with opioid therapy can be understood mechanistically as being off-target effects on the endogenous opioid system. They describe how our emerging understanding of the endogenous opioid system might allow us to better understand how exogenous opioids can "hijack" this system to produce unexpected and undesired consequences, both when they are used for pain relief, and when they are misused or abused. They especially focus on how acute or chronic opioid therapy (COT) may impair some of the nonanalgesic functions of the endoge-

These issues of excess death and addiction, combined with a lack of any evidence of long-term efficacy,[3] have led many of us in the pain field to question whether opioid should ever be used to treat chronic nonmalignant pain. We know of some patients with chronic pain who are on long-term high-dose opioid therapy who are doing well (ie, have good pain control and good functional status), but these patients are exceedingly rare. Instead, we see large numbers of individuals who want to keep taking opioids, although after we assess them, we conclude that the long-term side effects of these drugs far exceed any benefit they are receiving.

This review highlights why we may see some of the more insidious problems that occur with COT, which are summarized below.

Individuals on COT may continue to "need" opioids to replicate the functions of endogenous opioids that are no longer being

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	Top down Functional Somatic Syndromes	Bottom up Central Sensitization
Resolves when nociceptive input removed	No	Yes
Sex ratio	Female>>Male	Female>Male
Age of onset of pain	Young – typically following puberty	Any age when ongoing nociceptive input occurs
Family history of pain	Yes	No
Psych co-morbidity	High	Moderate
Increased sensitivity to non-pain sensory stimuli	Yes	No
High number of functional somatic syndromes	Yes	No

Clauw DJ. Refresher Courses, 16th World Congress on Pain. 2016.

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And what about those patients already on opioids?

- A slow gradual taper of opioids rarely leads to worsening of chronic pain
  - Use the patients own history to point out that opioids have not improved pain and function, or are leading to intolerable side effects
- Discern what symptom(s) opioids are treating
- Consider opioid-sparing drugs
  - Cannabinoids
  - Mixed opioids (tapentadol, buprenorphin
  - Gabapentinoids

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Definitions

- Cannabis – A genus of flowering plants with three different species: indica, sativa, and ruderalis
  - Can be bred to have low amounts of psychoactive compounds (e.g. THC) that are used to make hemp, or high amounts that are used for recreational/medicinal purposes
  - Sativex is a oral spray that is a cannabis extract
- Cannabinoid – Compounds that act at cannabinoid receptors
  - Endocannabinoids – endogenous ligands produced naturally that bind to CB1 and CB2 receptors
  - Phytocannabinoids – plant origin (cannabis/marijuana)
    - At least 80 different cannabinoids in cannabis
  - Synthetic cannabinoids

CB, cannabinoid receptor; THC, tetrahydrocannabinol

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

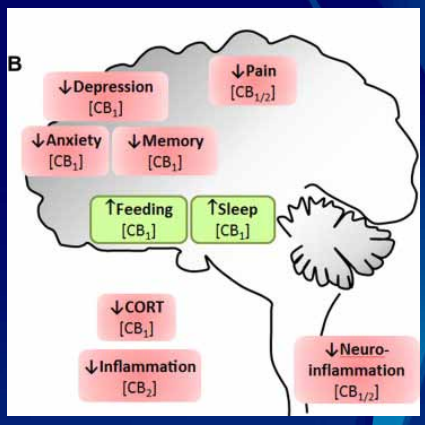
Cannabis-derived cannabinoids

More than 80 known, with different strains having different relative concentrations

- **THC** (Synthetic forms include Dronabinol, Marinol, Nabilone)
  - The primary psychoactive cannabinoid in cannabis, and its metabolites are those assayed for in drug tests
  - Although it binds relatively equally to both the CB1 and CB2 receptors, most of its effects are associated with CB1 activity in brain

CB, cannabinoid receptor; THC, Tetrahydrocannabinol

Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.



CB, cannabinoid receptor
Image source: © Crowe S, et al. Brain Behav Immun
Crowe S, et al. Brain Behav Immun. 2014;42:1-5.

Cannabis-derived cannabinoids

- **Cannabidiol** (CBD)
  - Is not psychoactive and does not bind with any significant affinity to CB receptors, but yet has anticonvulsant and anti-inflammatory effects
  - Is actually thought to potentially protect against psychoactive effects of THC and hypothesized by some to be an effective anti-psychotic (although a recent Cochrane review concluded there was insufficient evidence of this)
  - May act as a indirect antagonist of CB agonists – but it does not seem to reduce activity of THC
  - Also acts as 5HT1a agonist which might be responsible for potential analgesic, antidepressant effects

5HT1a, 5-hydroxytriptamine 1A receptor; CB, cannabinoid receptor; THC, tetrahydrocannabinol
Pertwee RG. Handb Exp Pharmacol. 2005;(168):1-51.

Proposed marketing program for medical cannabis

Cannabis plant talking to opium producing poppy plant

We don't suck as bad as you do

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Pragmatic Advice for Using Cannabinoids in 2018

- Where possible use a cannabinoid or cannabinoid extract of consistent and known potency
- Start with CBD alone and then go to low dose of low THC:high CBD strain and go up slowly
- Emerging evidence of U-shaped curve
- Oral dosing better once stable dose and strain identified
- The strongest recommendation based on current benefit: risk data is for the use of cannabinoids instead of opioids for neuropathic or centralized pain states
  - Data from US suggest that legalizing cannabis in a state leads to fairly dramatic reductions in opioid overdoses[1]
- Use with caution in individuals under age 25

CBD, cannabidiol; THC, tetrahydrocannabinol
1. Bachhuber MA, et. al. JAMA Int Med 2014;174:1668-73.

Treating Based on Mechanisms

Any combination may be present

	Peripheral (nociceptive)	Neuropathic	Centralized Pain
NSAIDs	+	-	-
Opioids	+	+	-
Surgery/ Injections	+	+	-
Tricyclics	+	+	+
SNRIs	+	+	+
Gabapentinoid	-	+	+
Cannabinoid	+	+	+

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Symptoms of Pain, Fatigue, etc.

- Nociceptive processes (damage or inflammation of tissues)
- Disordered sensory processing

Functional Consequences of Symptoms

- Increased stress
- Decreased activity
- Poor sleep
- Obesity
- Maladaptive illness behaviors

Dually Focused Treatment

- Pharmacological therapies to improve **symptoms**
- Nonpharmacological therapies to address **dysfunction**

Clauw and Crofford. *Best Pract Res Clin Rheumatol.* 2003;17:685-701.

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Nonpharmacological Therapies are similar to those for any Chronic Pain State

Strong Evidence	▪ Education ▪ Aerobic exercise ▪ Cognitive behavior therapy
Modest Evidence	▪ Strength training ▪ Hypnotherapy, biofeedback, balneotherapy, yoga, Tai Chi ▪ Neuromodulation
Weak Evidence	▪ Acupuncture, chiropractic, manual and massage therapy, electrotherapy, ultrasound
No Evidence	▪ Tender (trigger) point injections, flexibility exercise

Modified from Clauw *JAMA*. 2014

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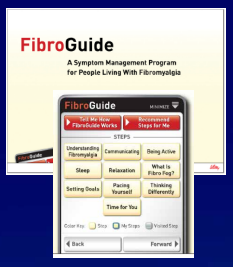
www.fibroguide.com



- Program features 10 CBT modules:
  - Understanding Fibromyalgia
  - Being Active
  - Sleep
  - Relaxation
  - Time for You
  - Setting Goals
  - Pacing Yourself
  - Thinking Differently
  - Communicating
  - Fibro Fog

- In a RCT of 118 FM patients comparing the earlier version of this website plus usual care, to usual care alone, Williams demonstrated statistically significant improvements in pain (29% in the WEB group had 30% improvement in pain vs 8% in usual care, p=.009) and function (i.e., 31% in WEB-SM had .5 SD improvement in SF-36 PF vs. 6% in standard care, p<.002) Williams et. al. Pain. 2010;151(3):694-702

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Summary

- Most practitioners have historically considered chronic pain to be largely from peripheral nociceptive input (i.e. damage or inflammation)
- When thinking about central factors in pain, many focus entirely on psychological factors
- We now understand that non-psychological central nervous system factors can markedly increase (sensitization) or decrease pain sensitivity
- The CNS is now thought of as "setting the volume control" or gain on pain processing and determining what nociception is felt as pain

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Summary

- The most highly prevalent pain conditions in younger individuals are now thought to be more "central" than "peripheral"
- Centralized pain or central sensitization can also be identified in subsets of individuals with any nociceptive or neuropathic pain state
- This is not currently appreciated in clinical practice so there is marked overuse of treatments for acute/nociceptive pain (opioids, injections, surgery, biologics, DMARDs) for treating centralized pain
- **Perhaps moving from considering FM a disease (i.e. the tip of the iceberg) to instead thinking of it as a CNS-driven *pathophysiological process* that can co-exist with any other disease or process would help the field, since current evidence strongly supports this notion**

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Osteoarthritis of the Knee – II

- Subsets of patients with OA of the knee display hyperalgesia and attenuated DNIC.[1]
- In past years, 2 classes of neuroactive drugs likely acting on volume control of pain processing have been shown to be effective:
  - Duloxetine (formerly tricyclic drugs had shown this same effect but have not gained wide usage)[2]
  - Tanezumab, a nerve growth factor inhibitor[3]
- Functional and structural neuroimaging results from Tracey group
  - Identify hyperalgesia/central sensitization in OA
  - Show that thalamic atrophy on VBM at baseline in knee OA normalizes following arthroplasty

1. Kosek E, Ordeberg G. *Pain*. 2000;88:69-78. 2-4. Clauw DJ, et al. Presented at: 2008 American College of Rheumatology Annual Meeting; October 24, 2008; San Francisco, CA; and 2008 International Association for the Study of Pain meeting; August 17, 2008; Glasgow, Scotland. 5. Gwilym et. al. . Arthritis Rheum. 2009 Sep 15;61(9):1226-34. 6. Gwilym et .al. Arthritis Rheum Vol. 62, No. 10, October 2010, pp 2930–2940

SELF EVALUATION

Chronic Pain Diagnosis and Treatment: Understanding the Underlying Mechanisms

1. Fibromyalgia or centralized pain patients are more frequently diagnosed with:

a. Irritable bowel syndrome
b. Tension headache
c. Temporomandibular disorder
d. Chronic fatigue syndrome
e. All of the above

2. Regarding the interplay between fibromyalgia and depression, which statement is not true

a. The rate of depression in fibromyalgia patients is somewhat higher than other chronic pain syndromes, but not overly so.
b. All antidepressants are effective in fibromyalgia
c. When using an antidepressant that has analgesic effects in fibromyalgia, the analgesic response to the drug is independent of the antidepressant response (i.e. people without depression respond just as well as those with depression).
d. Part of the reason for the higher incidence of depression and other psychiatric disorders in fibromyalgia is that there are shared neurotransmitters in pain and depression, and thus genetic polymorphisms affecting the binding or breakdown of these neurotransmitters would be expected to lead to a higher risk of any disorder that is caused by such abnormalities.

3. Classes of drugs that have been shown to be efficacious in fibromyalgia and other central pain states include:

a. Opioids
b. Compounds that raise both serotonin and norepinephrine
c. NSAIDs
d. Alpha -2-delta ligands (e.g. gabapentin, pregabalin)
e. b and d

4. Central nervous system neurotransmiter abnormalities that are present in fibromyalgia that likely correspond to effective treatments include:

a. Low serotonin and norepinephrine
b. High Glutamate
c. Low GABA
d. High Nerve growth factor
e. Low endogenous opioids

5. The clinical feaures of centralized pain include:

a. Multifocal pain
b. Fatigue
c. Sleep disturbances
d. Sensitivity to sensory stimuli
e. All of the above

6. T/F - Opioids are generally the most effective treatment for severe chronic pain

ANSWER KEY: 1. E, 2. B, 3. E, 4. E, 5. E, 6. F

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, *For Doctors Only: A Guide to Working Less and Building More*. 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.

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Wealth Planning for the 21st Century Physician: Residency to Retirement

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TODAY'S PRESENTATION

1. Background on physician stress
2. Risk management drill-down: social media
3. Asset protection background
4. Shielding cash flow and personal assets from potential risks

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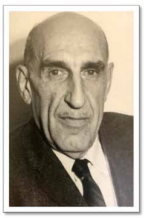
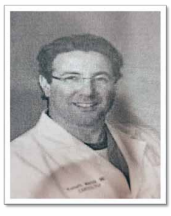
ABOUT ME





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PHYSICIANS STRESSED ABOUT LIABILITY

1. 87 percent of respondents said they are moderately-to-severely stressed/burned out on an average day.*
2. Concern about liability and lawsuits are a motivating force behind the skyrocketing costs associated with "defensive medicine"**
3. 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

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TYPES OF LIABILITY FACING PHYSICIANS

- Medical 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

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RISK MANAGEMENT VS ASSET PROTECTION

- Risk management: improve behaviors to reduce risk and potential liability
  - Category I CME Monograph: ***Risk Management for the Practicing Physician***
- Asset protection: shield assets in case of liability – recognition that there is always risk
  - Other books, including ***For Doctors Only***
  - New Title: *Wealth Planning for the 21st Century Physician: Residency to Retirement*

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RISK MANAGEMENT DRILL DOWN: SOCIAL MEDIA

- About 10% of physicians use social media – either to create/comment on content. Aesthetic specialties lead the way, but the numbers are growing…
- Benefits: establish the physician as a thought leader/expert.
- Risks: HIPAA violations for disclosure of protected health information (PHI);
- Related issue: Dealing with negative comments/complaints
  - Yelp, Doximity, Vitals, Healthgrades, etc.
- 2016 study on PubMed: "Social media use by physicians: a qualitative study of the new frontier of medicine"
- Need to create procedures/discipline; avoid reference to specific patient's case
- More on social media, texting, and other tech-based risk management in CME book

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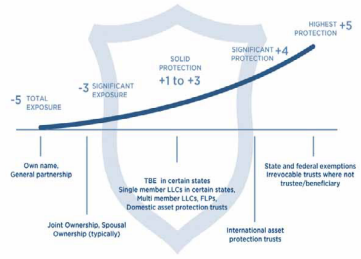
ASSET PROTECTION "SLIDING SCALE"



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

THE 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

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MAXIMIZE PROTECTIVE BENEFIT PLANS

- **Shields #1 asset – cash flow**
- Qualified retirement plans (QRPs) (+5)
  - Pensions
  - Profit-Sharing Plans
  - 401(k)s
  - 403 (b)s
- Significant other benefits: present tax deductions, long term tax growth/hedge, retirement, etc.
- *Defined benefit plans with buyout – some physicians can have tax benefits on front end (deductions) and back end (tax-free distributions)*

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QUALIFIED RETIREMENT PLANS (QRPs)

- If you are going to use QRPs, maximize your benefits:
  - Use proper formula to maximize what physicians can provide vs. employees
  - Be conscious of investment options and fees
  - Be careful of potential liability for under-performance of funds for employees as fiduciary
  - Investigate DB plans with partial buy-outs for tax benefits on front and back end

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WHAT ABOUT IRAs?

- Federal bankruptcy protection (+5)
- Varies widely among states
  - Ex. California
- In states where protections are weaker: Rolling into QRP?

OTHER BENEFIT PLANS

- Non-qualified plans – depends on plan/state
- Significant other benefits: present tax deductions, long term tax growth/hedge, retirement, etc.
- Can be structured for +2 to +5 protections, depending on state

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TITLING ASSETS: DOES IT PROTECT?

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

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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

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LLCS/FLPs (+2):
IDEAL FOR MOST ASSETS BEYOND EXEMPTIONS

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

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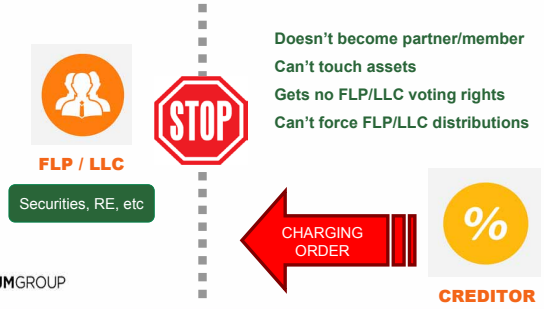
WHAT A *CHARGING ORDER* MEANS



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KEYS TO PROTECTION: FLPS/LLCS

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

- Key: experienced attorney who has annual monitoring/gifting plan

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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**
    - **12 states**
    - **"Hybrid" version for other states**
    - **Different than FLPs LLCs**

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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

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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

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ASSET PROTECTION
- LLCs
- FLPs
- TBE
- Trusts
- Debt Shields
- P&C Insurance
- Benefit Plans

CORPORATE STRUCTURE
- S CORPS
- C CORPS
- LLCs
- Partnerships
- Lease-backs
- Management Companies

RETIREMENT PLANNING
- Cash Flow Analysis
- Indexing Strategies
- Annuity Planning
- MRD Planning

INVESTMENT MANAGEMENT
- Asset Allocation
- Risk Assessment
- Stocks
- Bonds
- ETFs
- Commodities
- International
- Alternatives

TAX REDUCTION
- Multi-Entity
- Reasonable Compensation
- Qualified Plans
- Charitable Planning
- Tax Diversification

BENEFIT PLANNING
- Defined Contribution Plans
- Defined Benefit Plans
- Combo Plans

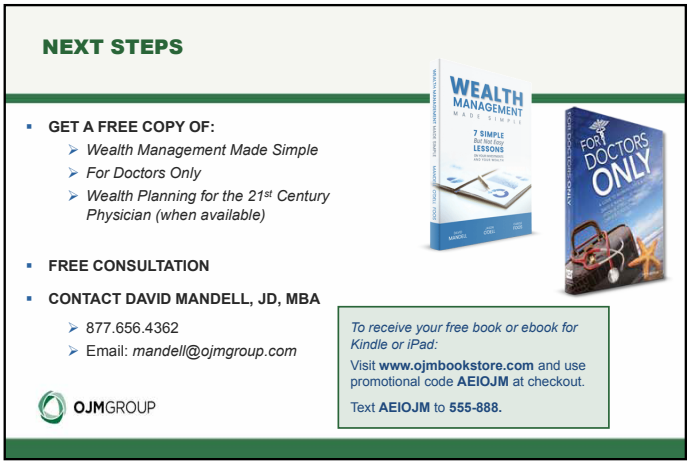
INSURANCES
- Term Life
- Permanent Life
- Individual Disability
- Group Disability
- Long-Term Care

HOW WE WORK WITH PHYSICIANS

SPECIAL OFFER:
FREE BOOKS FOR AEI SEMINAR ATTENDEES

- Text **AEIOJM** to 555-888.
- Click the link in the reply text.
- Choose your title and book format (hard copy or ebook for Kindle or iPad).
- Enter your name and contact information.
- Click SUBMIT.

OJMGROUP



SELF EVALUATION

Understanding Practice Risks and Protecting Assets Against Them

1. T/F - Concern about liability and lawsuits are a motivating force behind the growth of “defensive medicine.”

2. T/F - Medical malpractice is one of many potential liability sources for most doctors.

3. T/F - Asset protection is a discipline aimed at modifying behavior to reduce risk.

4. Risk management tactics to reduce potential HIPAA violations on social media DO NOT include:

a. Use of trusts
b. Avoiding discussion of existing patient facts
c. Having proper procedures for physicians and staff regarding social media

5. Which of the following asset protection tools generally get the top (+5) protective rating:

a. Family limited partnerships
b. Community property
c. Spousal ownership
d. State or federally exempt assets

6. Which are often called the “building blocks” of asset protection:

a. Non-qualified plans
b. Family limited partnerships and limited liability companies
c. Irrevocable trusts
d. Revocable trusts

7. T/F - Revocable trusts generally do not provide asset protection.

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

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Allan A. Anderson, MD, MMM, CMD, DLFAPA, of Cambridge, Maryland, is a board-certified psychiatrist with subspecialty certification in geriatric psychiatry. He is also a Certified Medical Director as well as Assistant Professor in Psychiatry at Johns Hopkins University School of Medicine. Dr. Anderson served as President of the American Association for Geriatric Psychiatry and in 2014 received the "Clinician of the Year" award from AAGP.

His practice centers around the evaluation and treatment of individuals with cognitive dysfunction including Alzheimer's disease and other dementias. Dr. Anderson has researched, written, and spoken extensively on topics associated with geriatric psychiatry, Alzheimer's disease in particular. He is also a speaker for Assurex Health.

You may contact Dr. Anderson with any questions or comments at 410-253-9697 or by email at geropsych@comcast.net.

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GERIATRIC AND FORENSIC PSYCHIATRY

Maintaining Brain Fitness

Question

Do you believe that it is possible to reduce your risk of being diagnosed with Alzheimer's or other dementias as you age?

1. Yes
2. No
3. Maybe

1

Who has experienced the following?

- You were just introduced to someone a few minutes ago and now you cannot remember their name
- You walk into a room to get something and can't remember what you are looking for
- You plan to stop at a store on the way home and instead go directly home
- You struggle to find a word that is on the tip of your tongue

Study of community dwelling older adults

- 67% reported that they had memory problems
- Only 6% stated they had memory problems compared to people their age

Salthouse, 1991

Major cognitive changes in normal aging

Reduced speed of information processing

Reduced working memory capacity

Reduction in some executive functions

Preserved semantic memory

*Vocabulary

*Accumulated knowledge

Some cognitive functions can improve with aging

Resilience

Stress tolerance

Compassion

Moutier CY et al. J Med Regulation 2013;99:10-18;
Meeks TW and Jeste DV. Arch Gen Psychiatry 2009;66

Brain Fitness Interventions

- To reverse or reduce the effects of normal aging
- To maximize cognitive functioning and enhance quality of life
- To prevent Alzheimer's disease and other memory impairing disorders

Factors effecting memory in normal adults

- Genetics
- Mood disorders
- Stress/Anxiety
- Medical diseases
- Medications
- Sleep
- Effort
- Attention
- Encoding strategies

Strategies to improve memory

Medications, vitamins, nutrients, herbal treatments and other supplements

Prescription Medications

- NMDA receptor antagonist (memantine)
- Acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine)
- May be effective if have diagnosis of dementia

No effect noted in normal adults

Hormone therapies

- Early interest in estrogen – studies not conclusive and potential risks
- Testosterone – Limited evidence, not scientifically proven, mostly anecdotal/small case studies

Medications that may adversely effect memory

- Medications with anticholinergic effects
- Sedating medications
- "Beers List" from the American Geriatrics Society (updated q 3 years?)

JAGS, 2015

Vitamins and Nutrients

- No evidence for any benefit of vitamin therapy with exception of the treatment of vitamin deficiency (B12/D) and hyperhomocysteinemia
- Omega 3 agents: Very limited data for any significant benefit

Other supplements

- No agents "proven" to have significant benefit and may have detrimental drug interactions
- Other agents may indeed be "snake oil" which prays upon a large population seeking some treatment for this common and debilitating disease

Ginkgo Biloba

- Large, well conducted study demonstrated no benefit
- No difference on any neuropsych tests as well as no difference in self or rater reports
- Side effects and drug interactions of some concern

Solomon et al, JAMA, 2002

Disease Management:
Treat Exacerbating Disease and Lifestyle Factors

- Depression
- Other psychiatric disorders
- Smoking/Substance Use
- Sleep disorders

Middleton and Yaffe. Arch Neurol. 2009; 66:1210-15;
Small: BMJ. 2002; 324:1502-5

Disease Management:

- Infectious disorders
- Post-surgical and post-anesthesia impairment
- Cardiopulmonary disorders
- Nutritional/Metabolic/ Endocrine Disorders
- Autoimmune/Collagen Vascular Diseases
- Normal Pressure Hydrocephalus
- Head Injury/Subdural Hematoma
- Neoplasms

Middleton and Yaffe. Arch Neurol. 2009;66:1210-15;
Small: BMJ. 2002: 1502-5

Do Cognitive Exercises Improve Memory?

ACTIVE* 2832 adults (age 65-94) randomized to:

*Memory training
*Problem solving training
*Training processing speed
*No training (control group)

Ball et al: JAMA 2002;288:2271-81; 2.
***A**dvanced **C**ognitive **T**raining for **I**ndependent and **V**ital **E**lderly

ACTIVE* 2832 adults (age 65-94)

Relative to control group, improvement seen in speed and problem-solving groups.

Memory gains not maintained at 2 years

Speed/Problem Solving gains maintained at 2 years

Ball et al: JAMA 2002;288:2271-81; 2.
***A**dvanced **C**ognitive **T**raining for **I**ndependent and **V**ital **E**lderly

ACTIVE at Follow Up

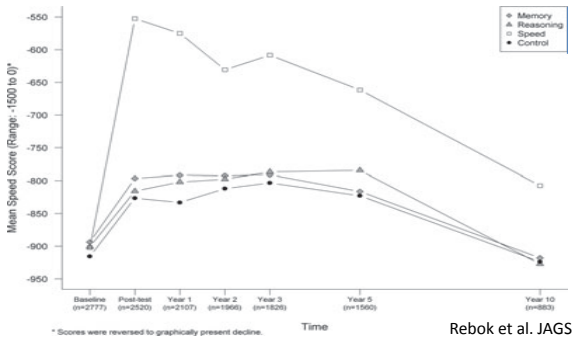
After 10 years:

*Gains in trained Reasoning and Speed held

*Self-reported Activities of Daily Living were at or above baseline (though not functionally tested)

Rebok et al. JAGS 2014

Speed of Processing Training Gains



Rebok et al. JAGS 2014

Do "Brain-Training" Programs Work?

Brain-training interventions improve performance on the trained tasks, less evidence that such interventions improve performance on closely related tasks, and little evidence that training enhances performance on distantly related tasks or that training improves everyday cognitive performance

Psychological Science in the Public Interest
Vol. 17(3). 103-186, 2016

National Institutes of Sciences, Engineering and Medicine
Preventing Cognitive Decline and Dementia: A Way Forward

CONCLUSION: Some RCT evidence suggests that cognitive training can delay or slow ARCD, as measured by performance on cognitive tests and instrumental activities of daily living. This conclusion is based largely on the ACTIVE trial.

CONCLUSION: There is no RCT evidence at this time that cognitive training will prevent, delay, or slow MCI.

June, 2017

MIND Diet

Mediterranean-DASH
Intervention for
Neurodegenerative
Delay

MIND Diet

Hybrid of Mediterranean and DASH

- Whole grains, green leafy and other vegetables, berries, fish, poultry, beans, nuts, olive oil
- Low in red meats, butter, margarine, cheese, sweets

Associated with:

- Slower cognitive decline
- Diminished association with Alzheimer's Disease

Prospective study of 923 subjects, age 58-95

Higher adherence to MIND diet decreased risk for onset of AD

Morris et al. Alzheimer's & Dementia 2015:1-8

You eat things from these 10 food groups

- Green leafy vegetables at least six servings per week
- Other vegetables at least one a day
- Nuts: Five servings a week
- Berries: Two or more servings a week
- Beans at least three servings a week

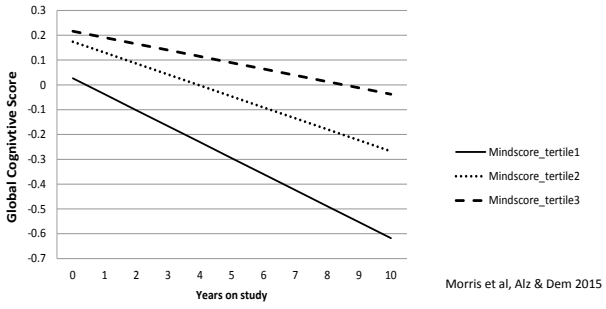
You eat things from these 10 food groups (cont'd):

- Whole grains: Three or more servings a day
- Fish: Once a week
- Poultry: Two times a week
- Olive oil: Use it as your main cooking oil.
- Wine: One glass a day

You avoid these food items:

- Red meat: Less than four servings a week
- Butter and margarine: Less than a TBS daily
- Cheese: Less than one serving a week
- Pastries and sweets: Less than five servings a week
- Fried or fast food: Less than one serving a week

MIND Diet Score and Cognitive Decline



Morris et al, Alz & Dem 2015

Alcohol?

Multiple studies find dementia risk reduction (40 – 80%) with mild-moderate alcohol use

- Most applicable to non-ApoEε4 carriers
- In ApoEε4 carriers even moderate alcohol use increases dementia risk.

Panza F et al. Alcohol consumption in mild cognitive impairment and dementia: harmful or neuroprotective? Int J Geriatr Psychiatry. 2012;27:1218-38.

Cognitive Decline is Associated with Alcohol Consumption in Midlife

Assessed cognitive functioning relative to alcohol consumption over a 10 year interval

No difference in cognitive decline up to 19.9 g/d of alcohol (8 g = 1 "unit")

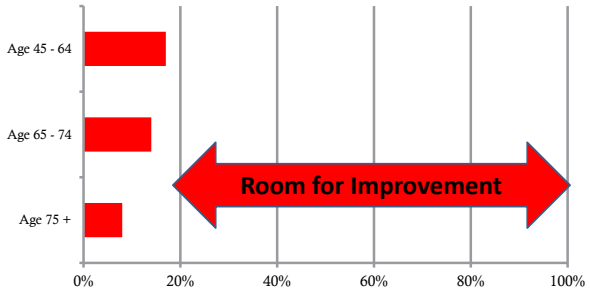
Consumption of ≥ 36 g/d alcohol in men, or ≥ 19 g/d in women, was associated with faster cognitive decline compared with light to moderate alcohol consumption.

Sabia et al. Neurology 2014;82:1-8.

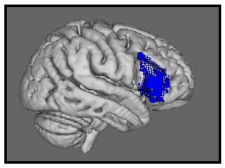
Physical Activity

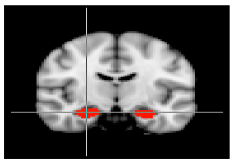
Exercise

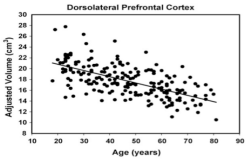
How Many U.S. Adults Meet Federal Guidelines for Suggested Physical Activity?

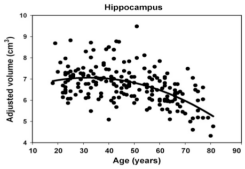


Blackwell et al. Summary health statistics for U.S. adults. National Health Interview Survey, 2012. National Center for Health Statistics. Vital Health Stat 10(260), 2012.





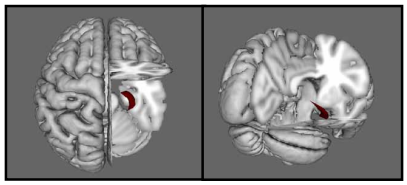


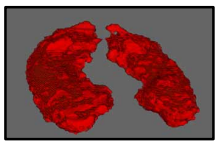


Kennedy, Erickson, Rodrigue, Voss, Colcombe, Kramer, Acker, Raz, 2009

Could cardiorespiratory fitness explain variation in hippocampal volume?

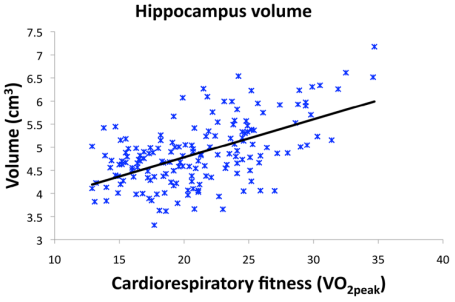
165 adults between 59-81 years of age, free of dementia
Spatial memory assessment
Aerobic fitness assessment (VO_2 peak) treadmill test.
MRI assessment with volumetric assessment of the hippocampal formation





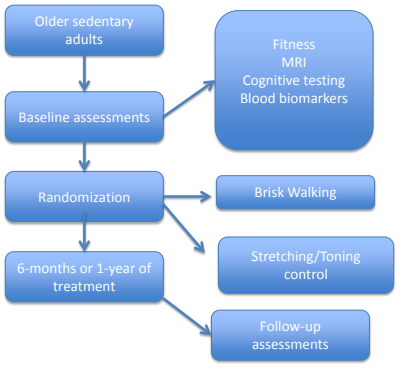
Erickson, Prakash, Voss, Chaddock, Hu, Morris, White, Wojcicki, McAuley, Kramer, 2009

Fitness and hippocampal volume



Erickson, Prakash, Voss, Chaddock, Hu, Morris, White, Wojcicki, McAuley, Kramer, 2009

Design of Exercise Intervention



Both groups receive physical activity around a track

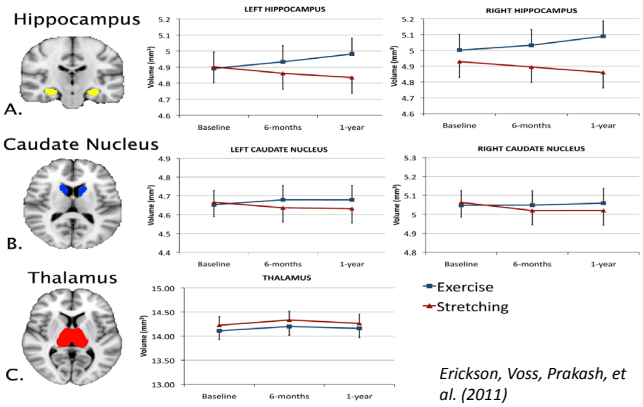
Both groups receive laboratory based treatment in groups

Both groups come to the lab 3 days per week for 30-45 minutes

Differences: Intensity and type of physical activity

	Walking Exercise	Stretching Control
N	60	60
Mean age (S.D.)	67.6 (5.81)	65.5 (5.44)
Sex (% female)	73%	60%
Attendance (%)	79.5% (13.70)	78.6% (13.61)
Fitness improvement (%)	7.78% (12.7)	1.11% (13.9)

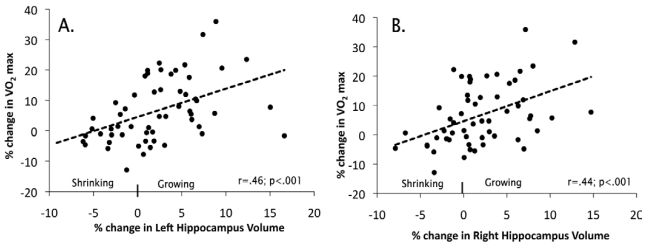
Erickson, Voss, Prakash, et al. (2011)



Erickson, Voss, Prakash, et al. (2011)

Are improvements in fitness associated with changes in volume?

Hippocampal volume increase correlates with increase in VO2 max



Erickson, Voss, Prakash, et al. (2011)

Effects of exercise in rodents

- Induces angiogenesis & neurogenesis
- Induces synaptogenesis
- Enhances learning and memory
- Increases production and secretion of brain-derived neurotrophic factor (BDNF) among others

General Conclusions

- Exercise has widespread effects on the brain.
- Moderate intensity exercise several days a week is sufficient for improving brain health.
- Starting to exercise in late life is not futile: even those who are sedentary can improve function.
- Exercise may have long term health consequences for diseases of the brain.

Many unanswered questions:

1. How long are the effects of exercise retained?
2. What types of exercise is most effective?
3. What are the dose-response effects?
4. What do volumetric differences reflect on a cellular level?

Sleep Changes with Age

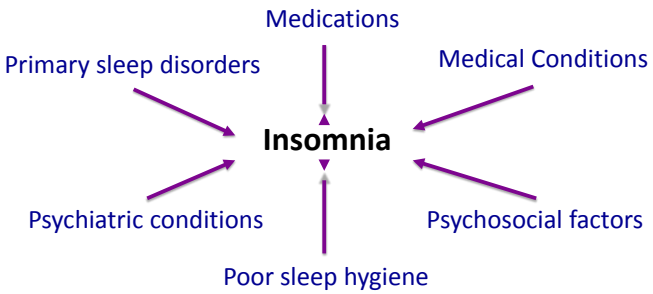
- Take longer to fall asleep
- Awake more frequently during the night
- Spend more time in bed
- Feel less rested, feel drowsier in the day time
- Nap more during the day time

Consequences of poor sleep

- Difficulty sustaining attention
- Slowed response time
- Impaired memory and concentration
- Higher incidence of depression and anxiety symptoms

Ancoli-Israel S, Cook JR. JAGs, 2005;53 (suppl):S264-S271

Address these factors to improve sleep



Other factors:

Social Engagement

Relaxation strategies

Maintaining a purpose in life

Social Engagement

- Isolation is a risk factor for health decline:
  - Increases risk for breast cancer in women
  - Impairs immune function
  - Boosts inflammation
  - Increases risk for arthritis, type II diabetes, and heart disease
  - Reduces survival after cardiac surgery.
- Isolated elderly adults are twice as likely to die prematurely

Cacioppo and Hawkley. Perspectives in Biology and Medicine 2003;46:S39-S52

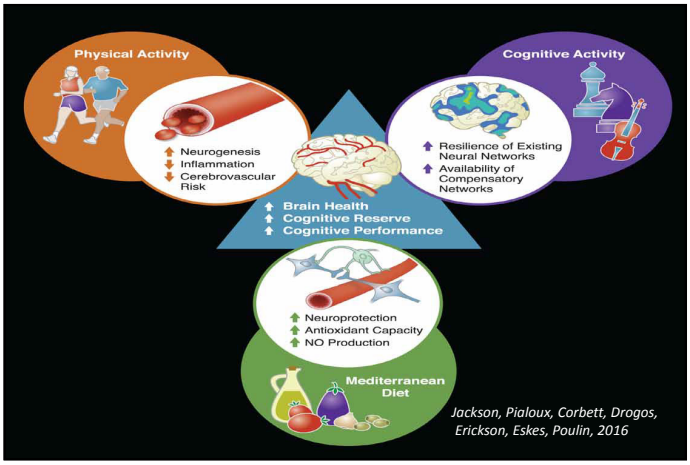
Relaxation / Meditation / Yoga

Benson RR improved attention but not other measures, small trial in older adults.[1]

Meditation improved attention and executive function.[2]

Hatha Yoga classes (3x/wk x 8 wk, n=118) were associated with improvement in working memory, set-shifting, mental flexibility.[3]

1.Galvin et al. Complement Ther Clin Pract. 2006;12:186-91; 2. Gard et al. Ann N Y Acad Sci. 2014;1307:89–103; 3. Gothe et al. J Gerontol A Biol Sci Med Sci 2014;69:1109-16.



FINGER

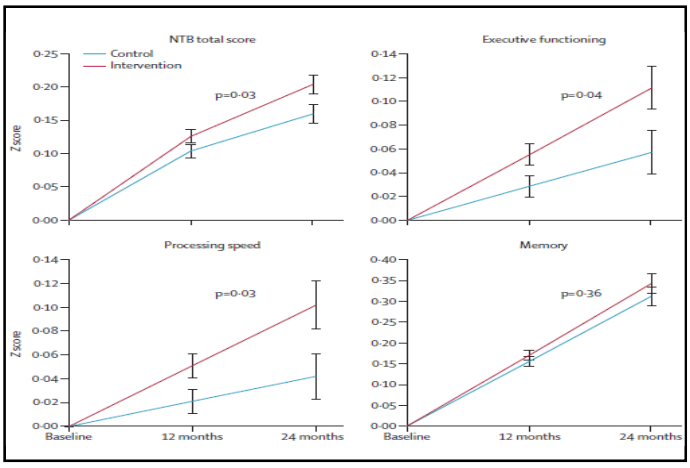
The FINGER study combined disease management (vascular), activity, nutrition, cognitive stimulation, social engagement.

2 yr RCT, n>1000, age 60-77

Control = health advice

Memory, executive function, processing speed, and composite evaluated at baseline and several subsequent visits.

Ngandu et al. The Lancet 2015;385:2255-22



LONDON, July 19, 2017 — The Alzheimer's Association announced the launch of a $20 million U.S. two-year clinical trial to test the ability of a multi-dimensional lifestyle intervention to prevent cognitive decline and dementia in 2,500 older adults with no current cognitive symptoms but who are at increased risk for later cognitive decline. The announcement was made at the 2017 Alzheimer's Association International Conference (AAIC 2017) in London. The large U.S. study to PrOtect through a lifestyle INTErvention to Reduce risk (US POINTER) will include physical exercise, nutritional counseling and modification, cognitive and social stimulation, and improved self-management of medical conditions. Recruiting for the study will begin in 2018.

Maintaining Your Memory

- Keep mentally active
- Keep physically active
- Keep socially active

Maintaining Your Memory

- Maintain good nutrition – MIND
- Control BP, Cholesterol other medical problems (take all medications as prescribed)
- Don't smoke
- Avoid excess alcohol

How to maximize memory and learning

- Make sure you can see and hear!
- Minimize distractions while learning
- Avoid alcohol and other drugs while trying to learn something new
- Avoid "cramming"
- Relax after learning

Other techniques

- Use mnemonic devices
- Create active pictures/stories
- Process material deeply
- "The Memory Book"

SELF EVALUATION

Maintaining Brain Fitness

1. Risk factors for Alzheimer's disease include all of the following except:

a. Positive family history
b. Presence of the ApoE3 allele
c. History of repeated head trauma
d. Presence of generalized vascular disease

2. T/F - Chronic use of benzodiazepines has been shown to increase the risk of Alzheimer's disease through a cause and effect relationship.

3. Which of the following diets have been observed to reduce cognitive decline and possibly reduce the risk of Alzheimer's disease:

a. The Grain-Brain diet
b. The Paleo Diet
c. A ketogenic diet
d. The MIND diet
e. Intermittent fasting

4. Studies conducted by Kirk Erickson and colleagues at the University of Pittsburgh have demonstrated the following brain changes related to physical exercise:

a. Increased total brain volume
b. Increased metabolic activity of the mammillary bodies
c. Cerebellar activation
d. Increase in volume of bilateral hippocampi
e. Frontal lobe activation

5. Studies of cognitive stimulation have demonstrated:

a. Improvements in generalized brain functions with use of cognitive games even in areas such as memory when the specific game did not focus on memory function
b. Improved language function
c. Improved hand/eye coordination
d. Improved gait speed
e. Improvements in the specific cognitive functions of the game, such as processing speed

6. Order of effect size from studies of lifestyle changes demonstrate an order of effect size as follows:

a. Socialization and diet > physical exercise and spirituality
b. Diet and spirituality > physical exercise and socialization
c. Physical exercise and diet > socialization and spirituality
d. Spirituality and physical exercise > diet and socialization
e. Physical exercise and spirituality > socialization and diet

7. Normal age related changes in cognitive function include:

a. Reduction in working memory
b. Reduced vocabulary
c. Reduced processing speed
d. Increased language disturbance
e. All of the above
f. a and c
g. a, b and c

8. Which of the below statements are true

a. Most studies of herbal and "memory pills" have limited scientific proof of any benefit in improving brain cognitive function
b. Acetylcholinesterase inhibitors have been shown effective in non-demented elderly with subjective memory impairments
c. Studies of exercise to prevent Alzheimer's disease have identified specific levels of intensity in order to achieve cognitive benefits
d. Intermittent fasting has been demonstrated to have no negative medical concerns

9. T/F - Approximately 40% of Americans over age 65 meet the federal guidelines for physical activity.

10. True statements about physical exercise and brain cognitive impairment include:

a. Equal benefits from aerobic exercise and resistance training
b. Increase in BDNF levels in animal studies
c. No significant effect if initiating exercise routines at a later age
d. Less benefit in improving cognitive function compared to brain stimulation exercises
e. Equal benefits of increasing hippocampal volume when comparing active physical exercise versus stretching

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

Daniel G. Pompa, DDS

Daniel G. Pompa, DDS, of Roslyn Heights, New York is a fellow of both The American Association of Oral and Maxillofacial Surgeons and The International Congress of Oral Implantologists. He has been a guest lecturer at Columbia University College of Dental Medicine and New York University College of Dentistry and is now a guest speaker at the University of Florida College of Dentistry, Boston University Henry M. Goldman School of Dental Medicine, University of Maryland School of Dentistry and the University of Pittsburgh School of Dental Medicine, among others. He has given over 600 lectures nationally and internationally, and in 2013 became a Seminar Series Speaker/ Consultant for the American Dental Association. Dr. Pompa has been published in such journals as *JADA* and *NYSAGD Journal* as well as *Dentistry Today* where he has been listed as a "Leader in Continuing Education." He is also an inventor, having been issued a U.S. Patent for his innovative work in the field of dental implantology.

You may contact Dr. Pompa with any questions or comments at (516) 287-0917 or by email at DPompaOMS@gmail.com.

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Medical Emergencies in the Healthcare Office: Prevention, Recognition and Preparation

3 Systems

- System I = Limbic Sys = ***Med Temp Lobe*** FAST Automatic, Emotional - **Right Side** 80% of the time
- System II = VentroMedial ***Pre-Frontal Cortex*** SLOW Cognitive, Deliberate, Analytical **Left Side** 20% of the time
- System III = allows switching from one to the other

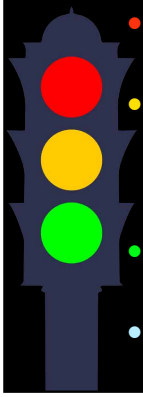
How we Respond to Stress…People involved:

- Cannon : 1929 Fight or Flight
- Laborit : 1986 Fight Flight or **Freeze**
- Renouard Article, 2017 on website
- Harvey: General DDS - 2018

To access the Pre Frontal Cortex:

- **(Stop)** Need to pause and regroup
- QRG / QRH - Color Coded Cards
- Focus (PFC cannot multi-task)
- One way to get into System II is by ***practicing mock drills*** allowing less Epi to block access to System III to allow a switch from Sys I to Sys II

Color Coding Emergencies



- WHITE=LOC=Syncope (Fainting)
- RED=Cardiovascular=Angina, M.I., Cardiac Arrest
- YELLOW=AC=Altered Consciousness-Insulin Shock= Hypoglycemia, Seizure, Hyperthyroid, Stroke, Drug Reaction, A.I., Hypotension
- GREEN=Allergic Reaction---Anaphylactic Shock
- BLUE=Respiratory=Hyperventilation, Asthma, Airway obstruction, P. E., C.H.F.

Ways to improve care in an emergency:

- **"Sterile Cockpit"** - restricts and forbids casual conversation during difficult or stressful stages of any procedure AND
- **"Checklist"** for Safety and Tasks —
- **"Closed-Loop Communication"**
- Gawande's book "The Checklist Manifesto" from on changed the way "things are done"

Results of Miller Study

- 83% of patients had 1 or more abnormal reading
- 1 in 5 patients had significantly abnormal readings, e.g. LFT and creatinine levels (Liver and kidney dysfunction)
- 50% of patients with *Cardio Vascular Disease, Diabetes or both* had abnormal kidney function-(Creatinine or BUN levels)

Effects of Age on Renal Function

- 1% of function is lost every year after 40
- Reduced ability to excrete drugs and metabolites -
- Elevated elimination half/time for many drugs including Anesthetics and Antibiotics
- CKD=GFR<60 for 3 months (> Creatinine Concentrations=<GFR)-requires dose reductions and/or lengthening dose intervals

Stages of Kidney Disease (CKD)

Stage 1: GFR 90 or greater (normal kidney function)
Stage 2: GFR 60-89 (mild decline in kidney function)
Stage 3a: GFR 45 - 59 (mild to moderate decline in kidney function)
Stage 3b: GFR 30 - 44 (moderate to severe decline in kidney function)
Stage 4: GFR 15-29 (severe decline in kidney function)
Stage 5: GFR < 15 = End Stage Renal Failure

< 60

Stages of Kidney Disease (CKD)

Stage 1: Creatinine levels: 0.5 - 1.3 ml/dl, males slightly >
Stage 2: Creatinine levels: 1.5 - 2.0 ml/dl
Stage 3: Creatinine levels: 2.1 - 5.0 ml/dl
Stage 4: Creatinine levels: 5.1 - 7.9 ml/dl
Stage 5: Creatinine levels: > 8.0 ml/dl

> 5

Effects of Age on Renal Function

- 1% of function is lost every year after 40
- Reduced ability to excrete drugs and metabolites -
- Elevated elimination half/time for many drugs including Anesthetics and Antibiotics
- CKD=GFR<60 for 3 months (> Creatinine Concentrations=<GFR)-requires dose reductions and/or lengthening dose intervals

Link for modification of dosage and/or interval for Rx for patients with CKD

CKD generally become prevalent when eGFR falls below 60 mL/min/1.73 m2 (stage 3 CKD or greater)

http://www.aafp.org/afp/2007/0515/p1487.html#afp20070515p1487-t8

IOS = Index of Suspicion

- Peripheral Numbness (18)
- Causes of Seizures (not form Epilepsy) (4)
- When to give Supplemental Oxygen (9)
- Causes of Syncope that are Iatrogenic (6)

Peripheral Numbness (18)

- Hypoglycemia*
- Hypothyroidism
- Hyperventilation*
- Hypertension*
- Hyperglycemia*
- Alcohol Abuse
- Stroke*
- Myocardial Infarction*

Peripheral Numbness

- Shingles
- Raynaud's Disease
- Lyme Disease
- Rheumatoid Arthritis, Lupus
- Vitamin Deficiencies: B1,B6,B12
- Toxins: Lead and Mercury
- Medications: Gabapentin and Amitriptyline, Metronidazole*
- Lymphoma and Multiple Myeloma

Unusual causes of LOC – as a first sign

- Hypoglycemia Unawareness
- UTI in elderly diabetic females

First sign (IOS) of a Medical Emergency:

- Altered Consciousness (AC) is almost always the earliest sign of a ***Medical Emergency***
- The earliest sign of altered consciousness is ***Confusion***

2014 Update on Basic Physical Diagnosis:

Reducing the Occurrence of Many Medical Emergencies in the Dental Office

Dr. Daniel G. Pompa

Oral and Maxillofacial Surgeon

Today there are many medically compromised patients coming to our offices. "The U.S. and global population demographics are constantly changing, chronic diseases are becoming more prevalent, new medications are being developed and brought to the market."[1] Many of these patients are often treated in dental offices without an adequate medical history and evaluation being taken prior to the onset of treatment.

It has been estimated that at least one or two office related deaths may occur during the career of a typical dental practitioner. These would not necessarily occur during the office visit, but could happen within 24 hours after the initial treatment.[2,3]

The overwhelming majority of medical emergencies that occur in dentistry happen during or immediately after local anesthetic administration. Anything a doctor can do to minimize stress at this time serves to prevent potential problems from developing.[4]"More

Periodontal Changes:

- ***"Evidence suggests that periodontal changes may be one of the first clinical manifestation of diabetes"***
- Lamster, Lalla, **JADA,** Vol 139, Supp 5, Oct **2008** pp19-24
- Since >33% of patients with DM don't know they have it and since more people see their DDS vs. their MD - (up to 70% vs. 40% of U.S. Population) ideally we should be on the forefront for screening for the disease and make the appropriate referral.

The prevalence of hypertension appears to be between 30–45% of the general population*

Classification of Hypertension			
Category	Systolic mmHg		Diastolic mmHg
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	**140–159**	and/or	**90–99**
Grade 2 hypertension	**160–179**	and/or	**100–109**
Grade 3 hypertension	180	and/or	110
Isolated systolic hypertension	140	and	<90

***Hypertension Volume 2013 (2013), Article ID 410740, 8 pages**

Review Article

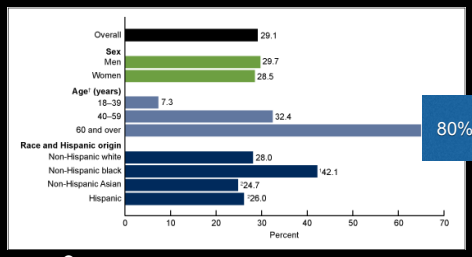
Hypertensive Patients and Their Management in Dentistry

Tuculina Ionela Dascalu

Worldwide incidence: 1 Billion

over 50% untreated
only 20% under control

Hypertension breakdown



- 55% (++) of HTN Population not treated and
- only 20% (-) of diagnosed HTN pt's are controlled.

Hypertension…

- One in three adult Americans have Hypertension
- 2/3's of individuals who have their first heart attack have Hypertension (69%)
- 3/4's of those who have a first stroke have Hypertension (77%)

Hypertension: Prevention

- AHA Recc: 1,500 mg. Sodium/day (average intake is 4,000 mg.)
- UK did a study from 2003-2011* whereby they decreased the consumption by 15% and found a 42% reduction in Stroke and 40% reduction in Heart Disease
- Note: only 10% of Sodium is in Salt we add

*British Medical Journal Open, April 14, 2014

AHA New Guidelines

- Was 140/90 = HTN
- Now 130/80 and over = HTN
- **120/80 = Pre Hypertensive!***

Whelton, Carey, Aronow. "Guidelines for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults"
J. Am Coll Cardiol: Nov. 16, 2017

The New Normal…

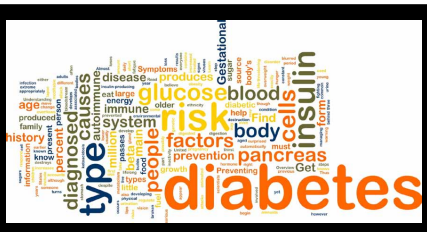
	Systolic	Diastolic
Normal	< 120	< 80
Pre-Hypertension	120 -129	< 80
Stage 1 Hypertension	130-139	80-89
Stage II Hypertension	>= 140	>= 90
Hypertension Urgency	>= 180	>=120
Hypertensive Emergency: 180/120 with Hx		

Hypertension

- Increasing Age will almost always cause an increase in Blood Pressure
- End organs of HTN are Brain, Heart, Kidney and Eyes.

End Organs for DM are:

- Eyes - Must be below 7 A1c
- Kidney - Must be below 7 A1c
- Cardiovascular - Must be below 6.5 A1c
- **Nerves: Neuropathy Must be below 7 A1c**
- **Teeth and Perio Disease**



- It is no longer a Cardiac Risk Factor it is now a
- Coronary Artery Disease Equivalent
- 10% of U.S. Population but
- Over 60 years old = 30% of population and
- 1/3 (33%) are not treated = 10 Million

Low Blood Sugar

- Average person with Type 1 DM experiences Hypoglycemia **up to 2 times a week**
- If untreated or ignored can lead to A/C, LOC, Seizures and Coma with potential for:
- Cardiac Arrest - Death

Other Hypoglycemia causes:

- not eating enough
- exercising more than usual
- drinking alcohol without eating food

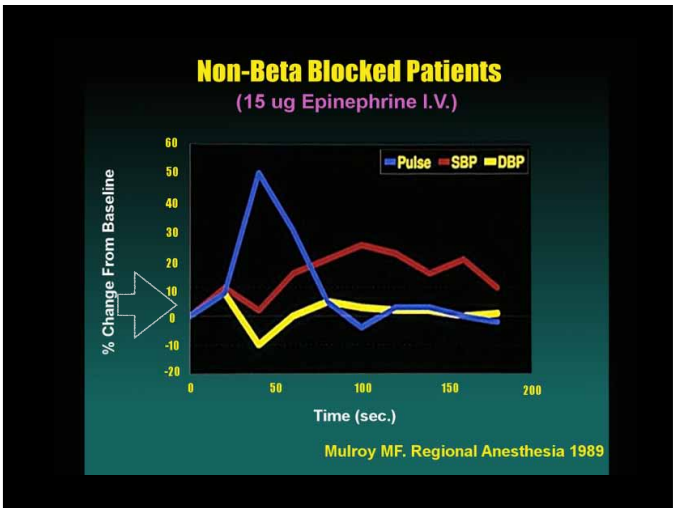
Adrenalin=Epinephrine

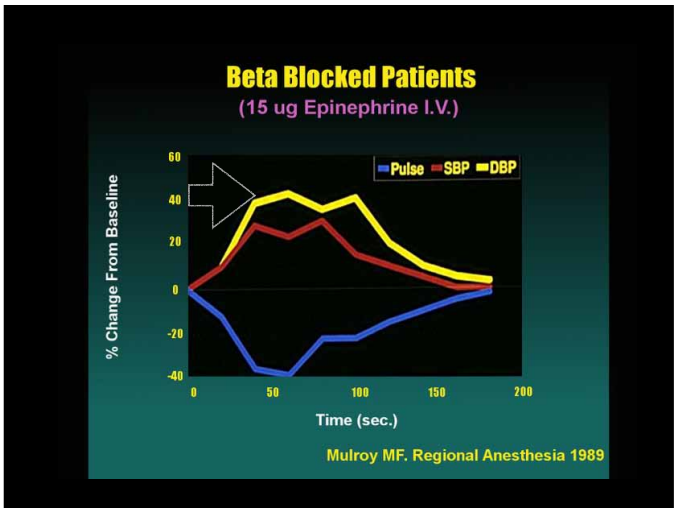
- B_1=directly increases heart rate and cardiac output..
- B_2=causes relaxation of smooth muscles in Lungs.....allowing open passages and more air exchange, and in the pupil—causes ciliary muscle relax - far vision focus and there is dilation of pupil
- A_1=causes contraction/constriction of peripheral smooth muscle in arterioles increasing blood pressure...

Templobe-memory = Amygdala Propranalol=Inderal (B1&2) can separate the anxiety, stress from the associated memory, if severely traumatic = can greatly lessen PTSD

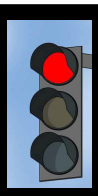
Careful use of Epi in LA for the following meds:

	BETA-ADRENERGIC BLOCKERS	Sympathomimetics epinephrine
OK	(a) Cardioselective (B1 only)	
	acebutolol	Monitan Rhotral Sectral
	atenolol	Tenormin
	metoprolol	Betaloc Lopressor
Caution	(b) Noncardioselective (B1 & B2 Blocked)	
	nadolol	Corgard
	oxprenolol	Trasicor
	pindolol	Visken
	propranolol	Inderal
	sotalol	Sotacor
	timolol	Blocadren Timoptic
OK	(c) Noncardioselective and alpha blocker	
	labetalol	Trandate





Red light flashing with following meds:



- ***Concerta, Methylphenidate***
- ***Cymbalta, Duloxetine***
- ***Seroquel, Quetiapine***
- ***Lexapro, Escitalopram***
- ***Neurontin, Gabapentin***
- ***Levaquin, Levofloxacin***

MEDICAL EMERGENCIES

- PREVENT
- PREPARE
- RECOGNIZE
- MANAGE

What we hear we forget..

What we see we remember....

WHAT WE DO WE KNOW.....

Legal and moral obligation of Healthcare Provider (Professional)....

- Is to keep the patient alive until either recovery occurs or until help arrives to take over management*

*Introducing: Blizzard Storm Scenario or B.S.S. = Hurricanes

Next 3 suggestions can reduce the occurrence of a major Medical Emergency

1) Taking a good history is the key to avoiding over 75% of all medical emergencies

2) Recording basic vital signs (BP, Pulse, Weight)

3) Giving great local and testing it will reduce medical emergencies.....

- because fear and unexpected pain can trigger:
  -Hypertensive Crisis -Hyperventilation
  -Asthmatic attack -Angina attack
  -Seizures -Syncope

Stress related Emergencies

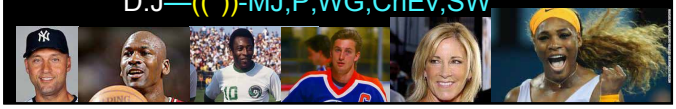
- Hypertension
- Hyperventilation
- Asthma
- Angina
- Anxiety Attack
- Seizures
- Syncope

We should all change our medical history page:

- Eliminate questions about Heart Murmurs
- ADD--Questions relating to Diabetes, ie It is no longer a Cardiac Risk Factor it is now a Coronary Artery Disease Equivalent
- Do you take meds for Osteoporosis?-ie Fosomax, Boniva, Actonal, etc.
- IV or IM injections once or twice per year?-ie-Zomada, Aridia and Reclast

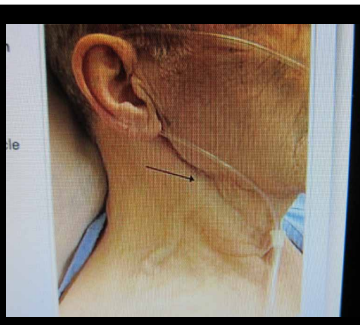
"Blink"

- author: **Malcolm Gladwell** (2005)
- Great decision makers are those who have perfected the art of "Thin-Slicing" = filtering the very few factors that matter from an overwhelming number of variables Goldman Cook County
- "Don't think-BLINK"
- D.J—((*))-MJ,P,WG,CriEv,SW



"Thin Slice-PD"

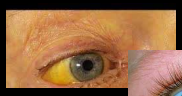
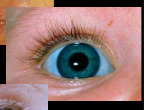
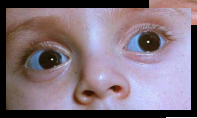
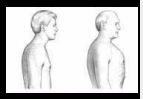
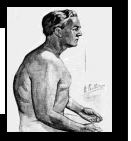
- gait of pt. walking into office
- eye contact or not=tension vs. relaxed
- shake hands = cold and dry vs. sweating and warm… (Hypothyroid vs. Hyperthyroid)
- face and forehead=cold, pale, sweating..pre syncope
- jugular vein distension - when upright, swollen ankles (CHF)
- breath sounds during conversation (Asthma)



With inability to walk up one flight of stairs + JVD = Oxygen

Exam at 20 paces…



- Color of Sclera in eyes
- Barrel Chest of COPD and Osteoporosis

Blue Sclera

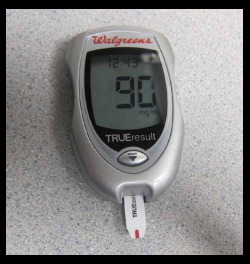
thinness of collagen fibers

- Hypothyroidism
- Osteogenesis Imperfecta (27)
- Marfans Syndrome
- Minocycline use (Tetracycline)
- Adrenal Insufficiency (Addison's Disease)
- Conjunctival Melanoma

CLINICAL CORRELATES

1.	Solitary submandibular node at angle of jaw.....	Nasopharyngeal carcinoma
2.	Osteoma of jaw.....	Gardner's syndrome
3.	Circumoral pigmentation.....	Peutz-Jeghers syndrome
4.	Odontogenic cyst in child.....	Basal cell nevus syndrome
5.	Giant cell lesion of jaw.....	Hyperparathyroidism
6.	Nodule in upper lip.....	Basal cell adenoma
7.	Loss of lamina dura.....	Hyperparathyroidism
8.	Ground glass.....	Fibrous dysplasia
9.	Parotid mass in a child.....	Capillary hemangioma
10.	Hair-on-end.....	Thalassemia
11.	Punched out lesions of bone.....	Multiple myeloma
12.	Radiolucency below the inferior alveolar canal....	Static bone defect
13.	Floating teeth.....	Histiocytosis X
14.	Butterfly rash.....	Lupus erythematosis
15.	Target lesions.....	Erythema multiforme
16.	Cafe-au-lait.....	Fibrous dysplasia Neurofibromatosis
17.	Cotton wool.....	Paget's
18.	Precocious puberty.....	Albright's syndrome
19.	Port wine stain.....	Sturge-Weber syndrome
20.	Amyloidosis of tounge.....	Multiple myeloma
21.	Sunburst.....	Osteosarcoma
22.	Lichen planus.....	Diabetes
23.	Deep voice.....	Hypothyroidism
24.	Solitary loose tooth.....	Cancer
25.	Funnel shaped alveolar canal.....	Neurofibroma
26.	White lesion in child.....	White sponge nevus
27.	Blue Sclera.....	Osteogenesis imperfecta
28.	Geographic skull.....	Hand-Schuller-Christian
29.	Paget's disease.....	Osteosarcoma
30.	Erythroplasia.....	Carcinoma-in-situ
31.	Hypercementosis.....	Paget's disease

CVS and Rite-Aid as well as:



Auto-BP

Pulse Oximeter

Rate Pressure Product

- (Systolic BP) X (Pulse) :
- If over 12,000 suggests compromised ability of coronary arteries to supply oxygen to myocardium*

The association of Rate Pressure Product and Myocardial perfusion imaging. Perfusion, 2012 May;27(3) 207-13 Ansari M Javardi H 10.1177/0267659112436631 Epub 2012 Feb 2

2016 Article

- "Pre-hypertension with coexistent higher body mass index (BMI) is significantly associated with increased myocardial oxygen consumption and hence more vulnerable to cardiovascular risks." *


*A comparative analysis of rate pressure product between prehypertensives and normotensives and its correlation with body mass index
Soundariya K1,*, Deepika V2, SP Venkatesh3
Indian Journal of Clinical Anatomy and Physiology, October-December 2016;3(4):452-455

HEART MUSCLE

- RBC's give up 30% of their Oxygen to tissue but the heart muscle takes out
- 60% of the oxygen so it needs it and is more susceptible to less Oxygen than other areas.

Oxygen as Premedication

- Any Patient with Angina
- If the RPP is over 12,000
- Oxygen Saturation is below 93%
- Patients with a history of seizures not responsive to meds
- Asthma and treated with Steroids and Anticholinergic meds
- History of CHF + JVD + Exertional Dyspnea
- Macho Man 16-30 years old - first visit for an extraction
- History of an MI in the past 6 months
- High BMI (over 30) with HTN

Four on the floor

- Asthma
- Angina
- Epilepsy
- Diabetes

Important questions to prevent emergencies:
Conversational History

- Do you drive? Diabetic or Epileptic patients who are not well controlled do not drive (assuming they knew how to), also Alcoholic patients may have their license revoked.
- Can you walk up a flight of stairs or walk one block without stopping? Do you need multiple pillows below your head to sleep?

- For Diabetic patients:
  Maturity onset or type 1?
  Did you take you meds today?
  Did you eat?
  Ever been in the hospital for problems?
- For Asthmatic patients:
  what type-allergic, environmental, emotional, Do you have your inhaler?
  Ever been in the hospital for problems?

- For Epileptic patients:
  what type? (Grand Mal or Petit Mal)
  what is your aura?
  how often and when was your last attack?
  Ever been in the hospital for problems?
- For Angina patients:
  what are your signs and symptoms?
  how often do you get them?
  what do you do? how often do you use nitro?
- Ever been in the hospital for any problems?

Simple tests in office

- Blood Pressure (screening and medico-legal requirement-PIL listed in all Locals)
- Pulse Oximeter (Pulse and O_2 Saturation)
- Glucometer (Blood Sugar levels)
- A1C (levels of blood sugar over 3 month period)

D_A_S_H_ the ABC'S
must ask questions **every time**

- Any New Drugs
- Any Allergies
- Any Surgeries
- Any Hospitalizations

D_A_S_H_ the ABC'S
must ask questions every time

- Any New Drugs
- Any Allergies
- Any Surgeries
- Any Hospitalizations
- Aspirin regimen or sensitive to it
- Any Bleeding disorders or history
- Chest Pain - any history of
- Shortness of Breath

More Medical Emergencies:

- are occurring today because patients we see today enjoy medical advances not known just 20 years ago....
- Patients on Plavix
- Patients with portable Oxygen
- Patients with implanted defibrillators

Age of Population

- As of 2014 46,200,000 million Americans are 65 or older
- Will double in the future - 25-30 years
- "This Population will present a much greater risk of a emergent CV event such as a MI or Stoke" (Chawla and Jaggi, 2016 Journal of Endocrinology and Metabolism)

Young Population

- Incidence of Asthma in children and young adults is increasing (over a 30% increase in last 20 years - as of 2016) CDC, 2016
- Alarming increase in the incidence of Type 2 Diabetes in children and adolescents with 1/3 of children as overweight and 17% are obese.
- "Both these groups are likely to experience serious health issues later in life"*

*Pulgaron, Current Diabetes Reports 2014
*World Health Organization, 2016

Physical inactivity remains high with 23.5% of adults reporting they've done no physical activity or exercise in the last 30 days; that level of inactivity has not changed appreciably for the last decade."

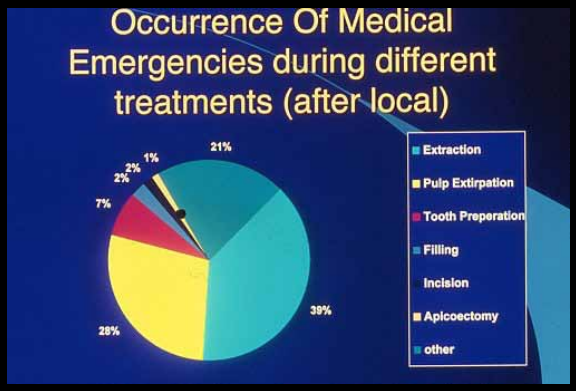
2015 American's Health Rankings - United Health Foundation

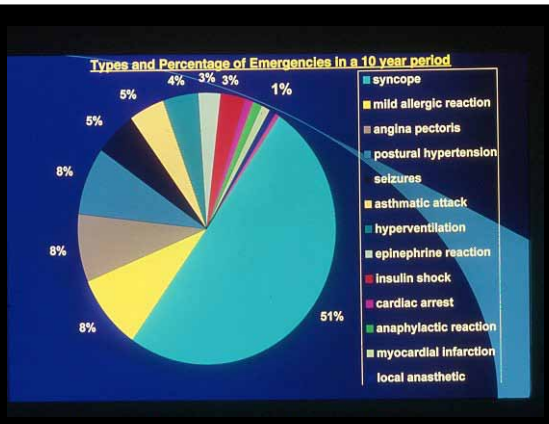
Increase in Obesity in the U.S. is now 29.9% of the adult population.

Diabetes Type II has also increased - up to: 10.5% of the U.S. adult population. (Doubled in 25 years).

Cardiovascular Deaths were decreasing in the U.S. for every year since 1993 until 2015 - now increasing over the last 2 years: up 2% from 250.8/100,0000 deaths to 254.6/100,000 deaths.

*2017 American's Health Rankings - United Health Foundation





Medical Office Emergencies*

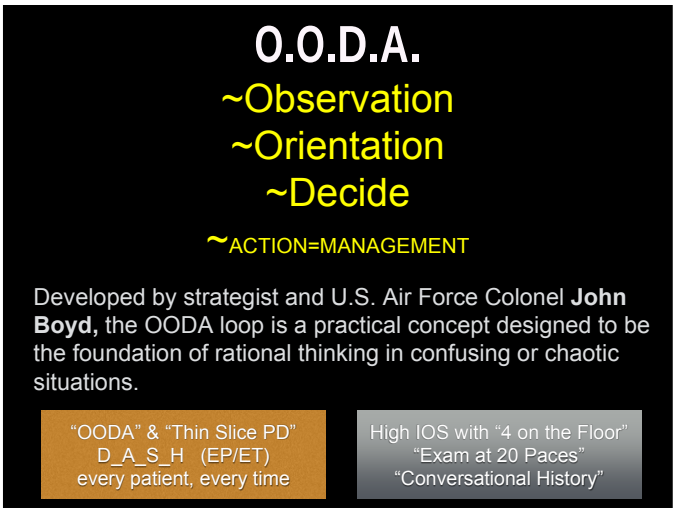
- 1) Asthma exacerbation
- 2) Psychiatric emergency, Anxiety Reax
- 3) Seizure
- 4) Hypoglycemia
- 5) Anaphylaxis
- 6) Altered Consciousness
- 7) Shock
- 8) Poisoning
- 9) Drug Overdose
- 10) Cardiac Arrest

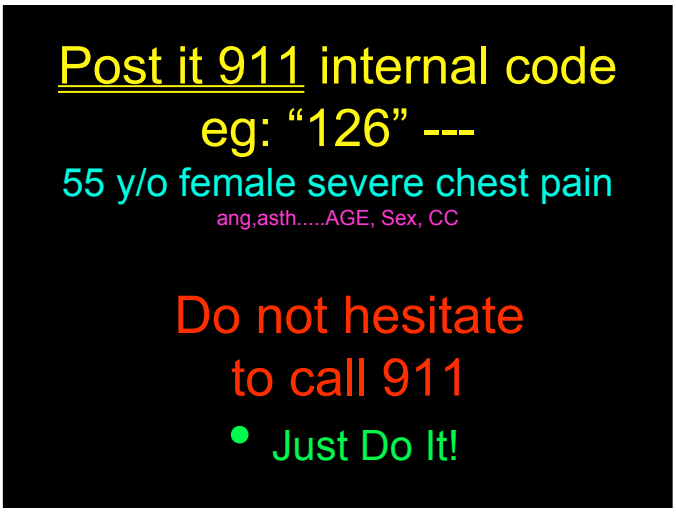
*Toback, S, MD. Medical Emergency Preparedness; American Family Physician;Vol 75,No.11,(2017),p1680-1684

Drugs/Supplies listed for a Medical Office Emergency Kit:

- Nebulizer
- Glucometer, Pulse Oximeter,
- IV equipment, Dextrose 25% solution
- Lorazepam (sublingual) Ativan (3-4mg)
- Flumazenil (Romazicon) (1.0 mg - IN)

*Toback, S, MD. Medical Emergency Preparedness; American Family Physician;Vol 75,No.11,(2017),p1680-1684





SELF EVALUATION

Medical Emergencies in the Healthcare Office: Prevention, Recognition and Preparation

1. T/F - An "E" Tank Cylinder for Oxygen should be in every Health Care Office

2. T/F - The most common Medical Emergency in a Medical Office is Asthma exacerbation?

3. What is the Rate Pressure Product?
   a. the sum of your pulse plus age
   b. the result of subtracting your age from your weight
   c. systolic blood pressure plus diastolic blood pressure
   d. the product of multiplying Systolic BP x Pulse Rate

4. What atypical signs and symptoms of having an Acute Myocardial Infarction (AMI) might present in females and females with Diabetes?
   a. Acute shortness of breath
   b. Unusual Fatigue
   c. Elevated blood sugar
   d. No chest pain experienced
   e. All of the above

5. What are the chances someone outside of a hospital setting would have of surviving Cardiac Arrest?
   a. 4%-6%
   b. 10%-15%
   c. 15%-20%
   d. 20%-25%

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

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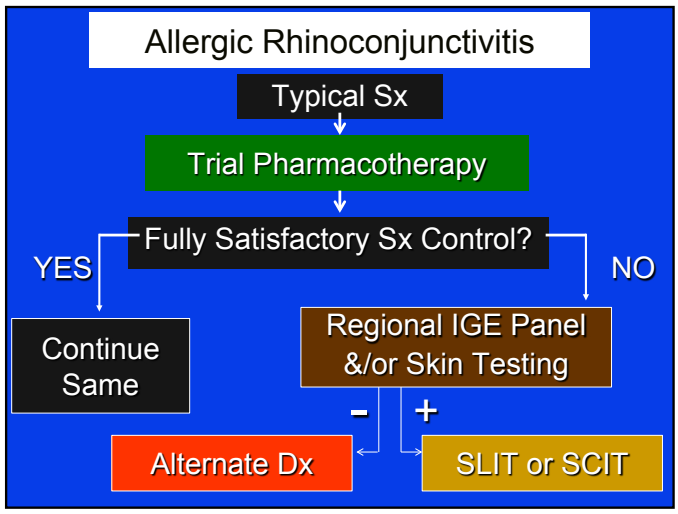
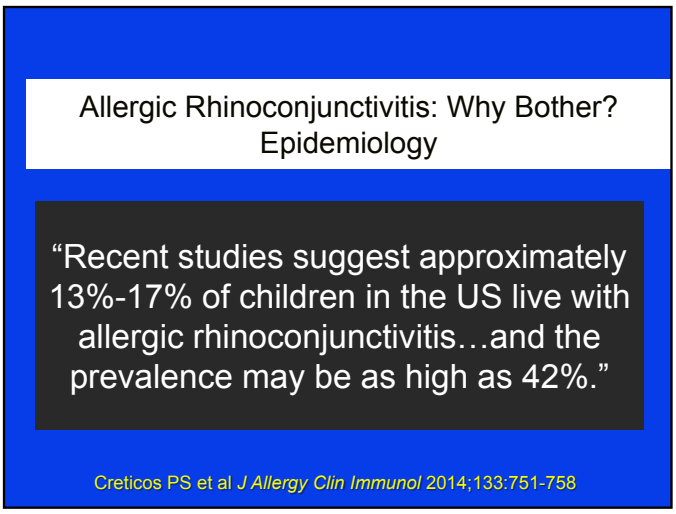
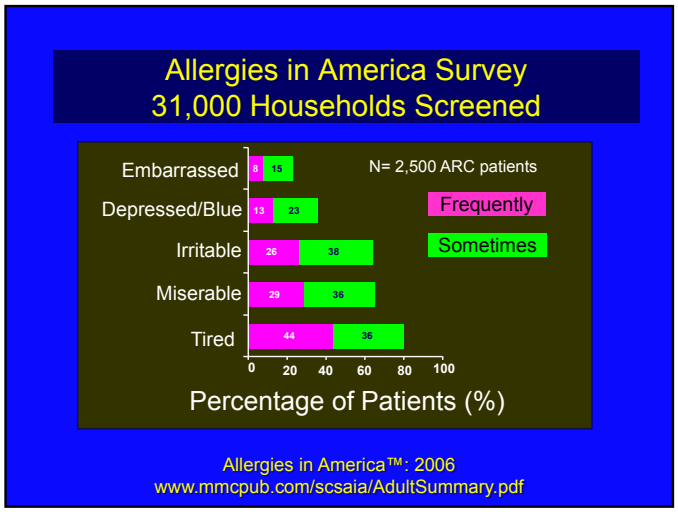
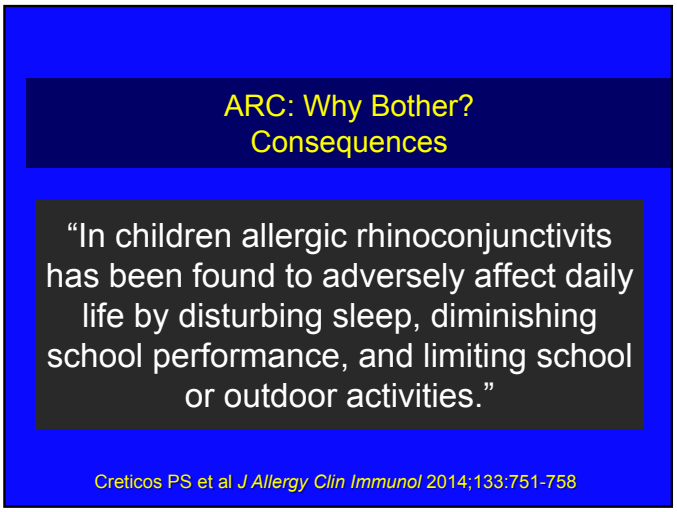
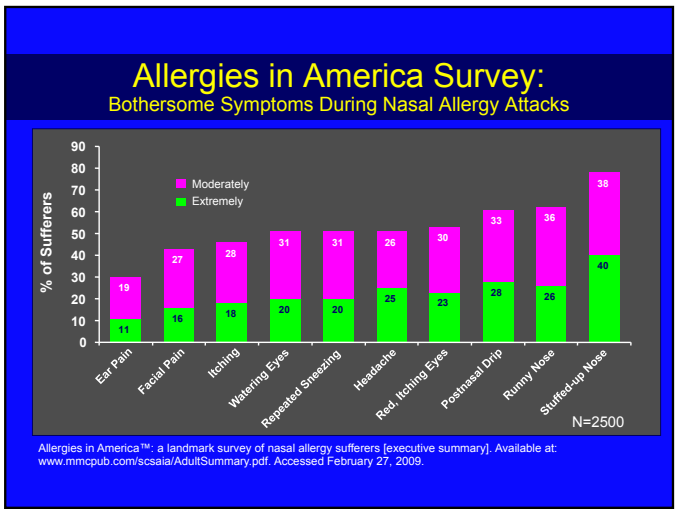
New Treatment Options for Allergic Rhinitis

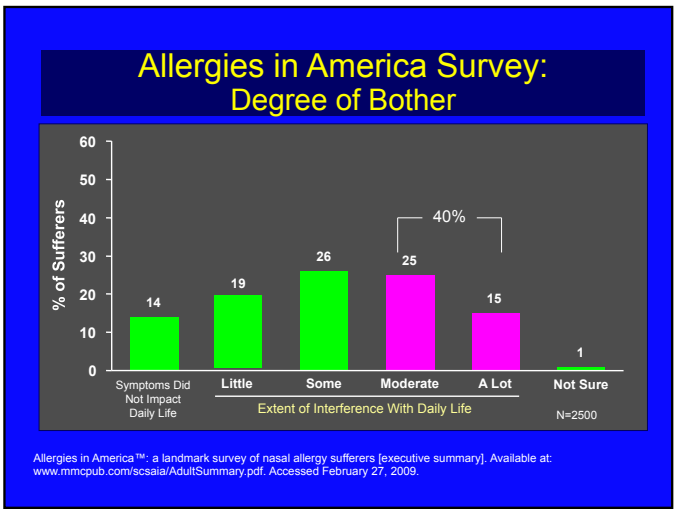




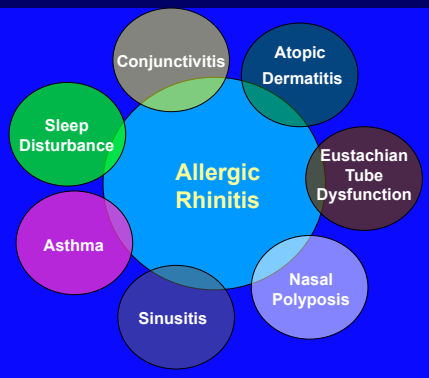








AR and Comorbid Disorders



ARC: Why Bother? Immunotherapy Benefits

- Improved QOL
- ↓ Risk of future sensitizations
- ↓ Risk of developing asthma
- Reduction in meds
- Disease modifying

Creticos PS et al *J Allergy Clin Immunol* 2014;133:751-758

USA Classification of ARC
An IgE-Mediated Allergic Response

Perennial Allergic Rhinitis (PAR)
[e.g., house dust]

Seasonal Allergic Rhinitis (SAR)
[e.g. ragweed]

Non-Allergic Rhinitis (NARES, VMR)
[e.g., perfume induced]

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

USA Classification of ARC
An IgE-Mediated Allergic Response

Seasonal Allergic Rhinitis SAR
- Sx periodic
- Sx related to seasonal variations airborne allergens
  - Grass Pollen
  - Tree Pollen
  - Weed Pollen
  - Fungal Spores

Perennial Allergic Rhinitis PAR
- Sx persistent
- Sx may fluctuate with exposure
  - Dust mites/Roach
  - Animal Dander
  - Perennial Pollens
  - Mold

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

Rhinitis Action Statements
American Academy of Otolaryngology

Hx & PE	Dx AR: Hx & PE consistent with allergies + ≥1 congestion, rhinorrhea, itch, sneezing, pale mucosa, tearing	
Allergy testing	Perform in nonresponders or 'need to know'	
Imaging	NOT if Sx consistent with AR	
Comorbidities	Identify asthma, atopic dermatitis, OSA, conjunctivitis, OM	

Seidman MD et al *Otolaryngol Head Neck Surg* 2015;52(1S):S1-S43

ARC: Characteristic Sx

Nose
- Watery rhinorrhea
- Nasal congestion
- Sneezing
- Itching
- Sinusitis

Throat
- Itch (pharynx, palette)
- PND
- Cough

Eyes
- Itching
- Watery discharge

Ears
- Itching
- Eustachian Tube Dysfunction

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

ARC: Differential Diagnoses

- Rhinitis medicamentosa
- Infectious rhinitis
- Anatomic obstruction
- Hormonal rhinitis
- Nonallergic eosinophilic rhinitis (NARES)
- Idiopathic nonallergic rhinitis
- Cribriform Plate Fx

Wallace DV, et al *J Allergy Clin Immunol* 2008;122(2 suppl):S1-S84 (adapted)

ARC Rx Choices

Disease Modifying Rx	Symptomatic Rx
• Sublingual Immunotherapy (SLIT) • Subcutaneous immunotherapy (SCIT)	• Nasal Steroids • Antihistamines • LKTRAs • Anticholinergics • Cromolyn

AR: Potential Rxs

- Allergen Avoidance
- Environmental Control
- Pharmacotherapy
- Toxin Avoidance (esp smoking)
- Hygienic measures (eg, nasal lavage)
- Immunotherapy
  - Subcutaneous (SCIT) aka 'Allergy Shots'
  - Sublingual tablets (SLIT)

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

Environmental Controls: SAR

- Avoid outdoor activities during times of high pollen counts
- Use air conditioning; keep windows closed
- Wear a face mask during outdoor activities (eg, lawn mowing)

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

Environmental Controls: PAR

- Humidity <50%(→↓ indoor mold)
- Dust mites: Hot wash bedding weekly
- Allergen-impermeable covers on pillow, mattress, box spring
- Remove pets/keep out of bedroom
- HEPA vacuuming of carpeting
- Wear face mask when house cleaning

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

House-Dust Mite Allergy
Couldn't You Just Use Avoidance Measures?

A Cochrane-based review of 54 RCTs explored the clinical impact of various avoidance strategies….no effect of control measures was found. The authors criticized current guidelines, suggesting that avoidance measure are not evidence based….."

Calderon MA, et al J Allergy Clin Immunol Pract 2015;3:843-855

Allergic Rhinitis Algorithm

Typical Sx

Symptomatic Rx

Anti Cholinergics (NS)	H1RA (NS)	H1RA (PO)	LKTRA	Steroids (NS)

ARC Symptomatic Rx Algorithm

- Steroids (NS)
- H_1RA (NS)
- LKTRA
- Anticholinergics (NS)
- Cromones (NS)

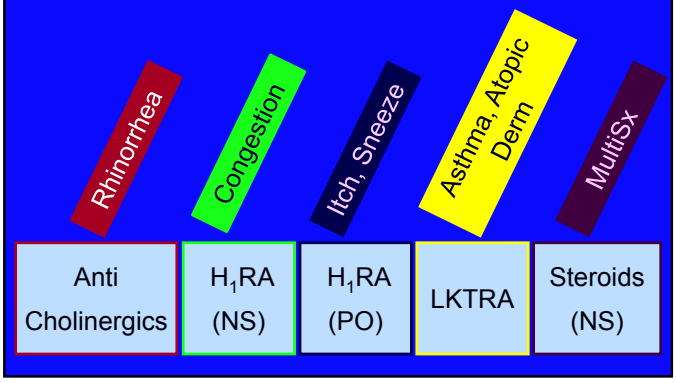
H1RA (PO)

Sx-Targetted Rx

	Blockage	Rhinorrhea PND	Sneeze	Itch
Steroid (NS)	+++	+++	+++	++
Antihistamine (PO)	+	++	+++	+++
Antihistamine (NS)	++	++	++	++
LKTRA	+	+	+	+
Anticholinergic	-	+++	-	-
Cromolyn (NS)	++	++	++	-

Seidman MD et al *Otolaryngol Head Neck Surg* 2015;52(1S):S1-S43 [adapted]

Allergic Rhinitis Algorithm: Sx Rx



Rhinitis Action Statements
American Academy of Otolarygology

Oral antihistamines	Use 2nd generation agents for sneeze/itch
Intranasal antihistamines	Appropriate for SAR, PAR, or episodic allergic rhinitis
Environmental	Option
LKTRAs	Not 1st line Rx
Combination Rx	OK if monotherapy insufficient
Immunotherapy	SLIT or SCIT when pharmacologic Rx insufficient

Seidman MD et al *Otolaryngol Head Neck Surg* 2015;52(1S):S1-S43

Rhinitis Action Statements
American Academy of Otolarygology

Surgery	Inferior turbinate reduction in pharmacology non-responders
Acupuncture	As per patient preference

Seidman MD et al *Otolaryngol Head Neck Surg* 2015;52(1S):S1-S43

Pharmacotherapy: H1RA

- 1st generation (eg brompheniramine chlorpheniramine, diphenhydramine)
  - Short acting
  - Sedation/Cognitive impairment
  - Anticholinergic

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

Pharmacotherapy: H1RA

- 2nd generation (eg, cetirizine, desloratidine, fexofenadine, loratadine, levocetirizine)
  - Long acting
  - No/Low sedation/cognitive
  - No meaningful anticholinergic

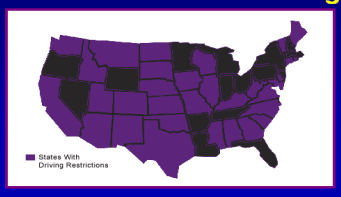
Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84 (adapted).

Cetirizine CNS Precautions

- Most common AE in patients > 12yrs: somnolence
- Somnolence Dose related
  - Placebo = 6%
  - Cetirizine 5 mg = 11%
  - Cetirizine 10 mg = 14%
- Caution operating hazardous machinery
- Avoid concurrent alcohol/CNS depressants

Zyrtec Prescribing Information

States With DUI Laws Concerning Any Drug



In 32 states and D.C, it is illegal to drive while impaired by meds. Definition of impairment varies by state—laws are written broadly and cover meds that are not specifically identified.

Sources: National Highway Traffic Safety Administration. *Digest of State Alcohol-Highway Safety Related Legislation*. 2002.

60

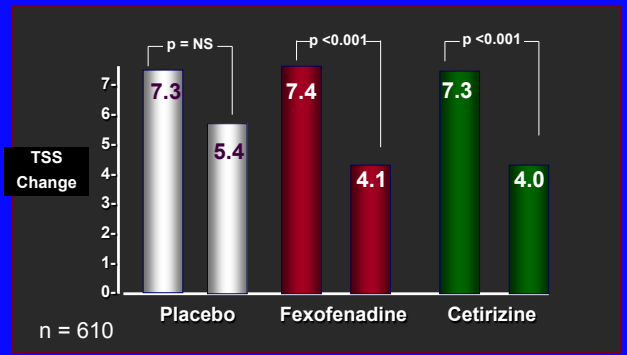
GLORIA Global Resources In Allergy™

SAR and H1RA Treatment Fexofenadine vs Cetirizine vs Placebo

- DBPCT (n=610) SAR patients
- Rx: Fexofenadine 180 mg/d vs cetirizine 10 mg/d vs placebo X 2 weeks
- 1^0 Outcome: Mean ▲ in Total Symptom Score
- Each Sx measured on 0-4 scale
  - Sneezing
  - Rhinorrhea
  - Itchy nose, Palate, or throat
  - Itchy, watery or red eyes

Howarth PH, et al J Allergy Clin Immunol 1999

Fexofenadine vs Cetirizine vs Placebo Total Sx Score at 2 Weeks



Howarth PH, et al J Allergy Clin Immunol 1999

Intranasal H_1RA: Potential 1st Line

- ≥ 2nd gen H_1RA for SAR (May be used as 1st-line Rx)[1]
- Clinically significant effect on congestion[1]
- May have some anti-inflammatory effect[2]
- Efficacy < nasal steroids[1] but
  - Quicker onset than nasal steroids [3]

1.Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84
2.Corren J, et al. *Clin Ther.* 2005;27:543-553 3. Kaliner M. *Ann Allergy Asthma Immunol.* 2007;5:383-391

ARC: Nasal Steroids

"Intranasal corticosteroids are the mainstay of Rx for AR….Their onset of action can be <30 minutes, although peak effect ay take several hours to days, with maximum effectiveness usually noted after 2-4 weeks….."

Sur DKC, Plesa ML *Am Fam Phys* 2015;92(11):985-992

Intranasal Corticosteroids

- Most effective medications for ARC Rx
- Reduce sneezing, itching, rhinorrhea, and congestion
- AEs (generally minimal), include stinging, burning, dryness, sneezing, epistaxis
  - Remember 'cross-hand technique'

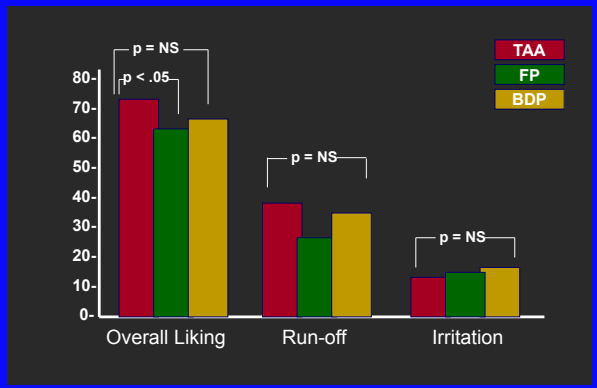
Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

Nasal Steroids: Pt Preferences

- STUDY: preference comparison of nasal steroids
  - Triamcinolone Acetate (TAA) 55 mcg/spray
  - Fluticasone Propionate (FP) 50 mcg/spray
  - Beclomethasone Diproprionate (BDP) 42

Gerson et al J Sensory Stud 1999;14:491-496

Nasal Steroids: Pt Preferences



Gerson et al J Sensory Stud 1999;14:491-496

ARC: BEST Nasal Steroid?

"There is no evidence that one intranasal corticosteroid is superior."

Sur DKC, Plesa ML *Am Fam Phys* 2015;92(11):985-992

Nasal Steroids Are There *ANY* Differences?

Agent	Advantage
Budesonide (Rhinocort Aqua)	Pregnancy Cat B
Triamcinolone acetonide (Nasocort)	OTC
Fluticasone furoate (Flonase)	OTC

Sur DKC, Plesa ML *Am Fam Phys* 2015;92(11):985-992

Other Pharmacotherapies

MAST CELL STABILIZERS[1]

- Not as effective as intranasal corticosteroids
- Prevent and relieve AR symptoms
- Side effects include sneezing, burning

LEUKOTRIENE-RECEPTOR ANTAGONISTS[2]

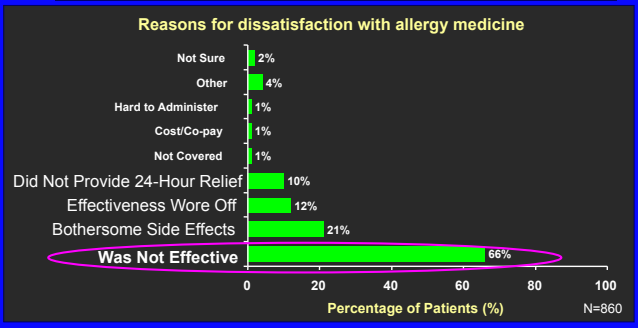
- No significant difference in efficacy with H1RA
- Less effective than intranasal corticosteroids

INTRANASAL ANTICHOLINERGICS[1]

- Excellent for rhinorrhea
- Side effects: nasal dryness, bloody nasal discharge

1. Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.
2. Nathan RA. *Ann Allergy Asthma Immunol.* 2003;90(2):182-191.

Allergies in America Survey: AR Sufferers Are Dissatisfied



Allergies in America™: Survey 2006

Case Study: Anna B, a 42 y.o. Female

- Hx: SAR began age 13
  - Sx every spring: sneezing
- Usual Rx: OTC antihistamines
  - 'not working this time'
- New Complaints This Year
  - Constant blocked nose
  - Husband complains of snoring
  - AM fatigue
  - Itching eyes/nose
  - Dark circles under her eyes

Case Study: H & P

- Sx:
  - Year-round: mild-moderate
  - Spring: mod-severe in the spring
- Allergic shiners, allergic crease
- Severe nasal blockage/congestion with boggy pale turbinates
- Postnasal drainage

Case Study: Clinical Dx

- Clinical Dx: mixed ARC (SAR+PAR)

NEXT STEPS

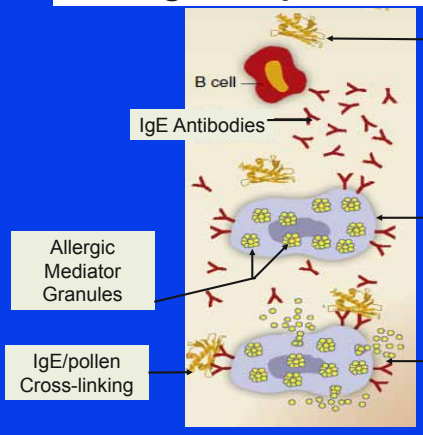
- Advance intensity of pharmacologic Rx
- You offer the option of Allergy Testing
  - Skin testing
  - Serum IgE testing (Regional IgE Panel)

Wallace DV, et al. *J Allergy Clin Immunol.* 2008;122(2 suppl):S1-S84.

Case Study: Lab

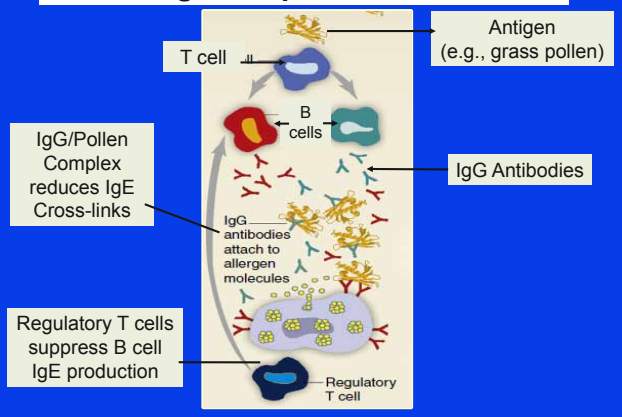
- Regional IgE Panel
  - ++++ House Dust Mite
  - ++++ Timothy Grass
  - Total IgE Elevated
- Dx: SAR + PAR

Allergic Response: Pre-Rx



Larsen JN, et al *Drug Discovery Today* 2016;21(1):26-37

Allergic Response: Post-Rx



Larsen JN, et al *Drug Discovery Today* 2016;21(1):26-37

Currently Available FDA-Approved Agents SLIT

Trade (age)	Contents	Indication: Allergic rhinoconjunctivitis Sx with + Skin test or IgE ab to….
Grastek (5-65 yrs)	**Timothy Grass**	**Timothy grass (or cross-reactant)**
Oralair (10-65 yrs)	**5 Grasses**	**Sweet Vernal, Orchard, Timothy, Perennial Rye, Kentucky Blue Grass**
Ragwitek (18-65 yrs)	**Short Ragweed**	**Short ragweed**
Odactra (18-65 yrs)	**House dust mite**	***D. farinae or D. pteronyssinus***

Immunotherapy for Asthma & Allergic Rhinitis Allergy Shots (SCIT) or Sublingual (SLIT)?

"…a growing body of evidence from DBPC studies shows that both SLIT and SCIT are effective in reducing Sx scores and medication use, improving QOL, and inducing favorable changes in specific immunologic markers."

Jutel M "Allergen-Specific Immunotherapy in Asthma"
Curr Treatment Options in Allergy 2014;1:213-219

SLIT Timothy Grass Children & Adolescents

- Study: DBRPCT children/adolescents with allergic rhinoconjunctivitis Sx with or without asthma (n = 345)
- Rx: Timothy grass tabs vs placebo
- Outcome: Total combined score

Blaiss M et al *J Allergy Clin Immunol* 2011;127:64-71

SLIT Timothy Grass Children & Adolescents

- Inclusion:
  - Age 5-17 years
  - Grass-induced allergic rhinoconjunctivitis
  - + skin prick test for timothy grass (5 mm > saline control)
  - + *P pratense* IgE (0.7 kU/L)
  - FEV1 ≥70% predicted

Blaiss M et al *J Allergy Clin Immunol* 2011;127:64-71

SLIT Timothy Grass Children & Adolescents

- Exclusions:
  - Perennial allergic rhinoconjunctivitis
  - Comorbid allergy to substance overlapping timothy grass season
  - Immunosuppressive Rx within 3 months
  - Hx of persistent severe asthma
  - Chronic urticaria/angioedema
  - Severe atopic dermatitis
  - <4 points ↑TCS in 1st 2 days of season

Blaiss M et al *J Allergy Clin Immunol* 2011;127:64-71

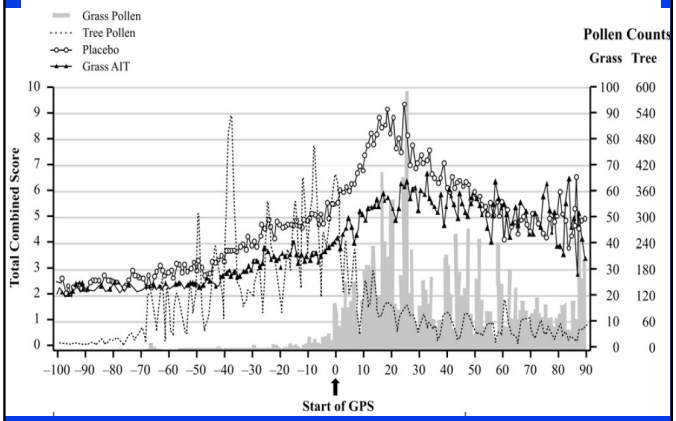
SLIT: Timothy Grass

Grass Season

- Start: 1st 3 consecutive days of pollen count > 10 grains/m^3
- End: last 3 consecutive days of pollen count >10 grains/m^3

Blaiss M et al *J Allergy Clin Immunol* 2011;127:64-71

Timothy Grass SLIT: Children & Adolescents



Blaiss M et al *J Allergy Clin Immunol* 2011;127:64-71

Timothy Grass SLIT in Children & Adolescents Safety

"…grass AIT was well tolerated, with oral pruritus and throat irritation being the most common AEs…and do not usually result in medication discontinuation."

Blaiss M et al *J Allergy Clin Immunol* 2011;127:64-71

Timothy Grass SLIT in Children & Adolescents Local Adverse Effects

- Most common on days 1 & 2 of Rx
- Duration average = ±16 minutes
- Remits without discontinuing Rx

Blaiss M et al *J Allergy Clin Immunol* 2011;127:64-71

SLIT: Ragweed

"SLIT represents an alternative mode of Rx that may afford a safe, convenient, and effective Rx modality for the management of allergic respiratory disease."

Creticos PS et al J Allergy Clin Immunol 2014;133:751-758

SLIT: Ragweed

- Study: RDBPCT adult rhinoconjunctivitis patients (n = 429) in USA and Canada with ragweed sensitivity
- Rx (±12 weeks): SLIT vs placebo
  - Initial Rx 8-16 weeks pre-season
  - Rx maintained through season
- Outcome: TCS (Total combined daily rhinoconjunctivitis Sx and Med Score)

Creticos PS et al J Allergy Clin Immunol 2014;133:751-758

SLIT Ragweed: Administration

- Run-in (all subjects): single-blind placebo
  - SL drops held under tongue X 2 mins, then swallowed
  - AE response to placebo → D-C
- Active Rx
  - 1st dosing in clinic on day 1, then home
  - F/U q 30 days

Creticos PS et al J Allergy Clin Immunol 2014;133:751-758

SLIT Ragweed: Season Identification

- Start: 1st day ragweed pollen count > 10 gr/m^3
- End: 1st 3 consecutive days ragweed pollen counts < 5 gr/m^3
- Peak: max 3 noncontiguous peak weeks

Creticos PS et al J Allergy Clin Immunol 2014;133:751-758

SLIT Ragweed: Inclusion Criteria

- Adults: 18-55 years
- Allergic rhinoconjunctivitis Sx X ≥2 years sufficient to require antiallergy meds
- + ragweed allergy skin prick test

Creticos PS et al J Allergy Clin Immunol 2014;133:751-758

SLIT Ragweed: Exclusion Criteria

- Hx anaphylaxis
- Hx persistent or unstable asthma
- ARC Sx attributable to perennial allergens overlapping ragweed season
- Inability to tolerate full-dose Rx on day 1

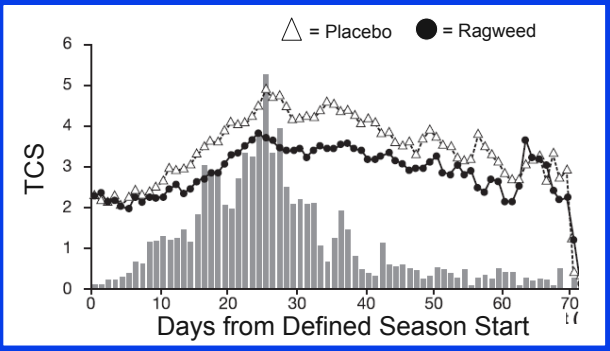
Creticos PS et al J Allergy Clin Immunol 2014;133:751-758

SLIT Ragweed Outcome: Total Combined Score (TCS)

- Recorded daily (A.M. & P.M.) in electronic diary, 0 (no Sx) to 3 (severe Sx)
  - Ocular: itch, swelling, redness, tearing
  - Nasal: sneezing, itch, rhinorrhea, blockage
  - Aural: itch
- Med Score:1 point for each daily use of loratadine, olopatadine, or albuterol inhaler
- TCS min clinically important difference = 20%

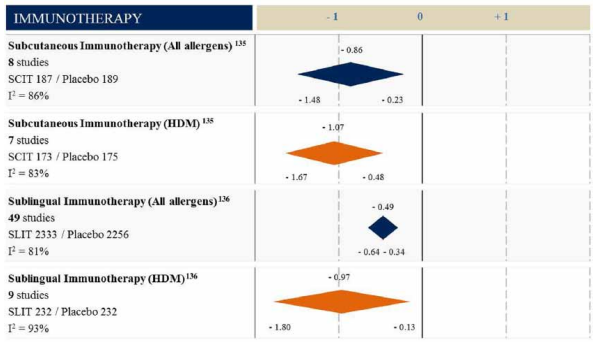
Creticos PS et al J Allergy Clin Immunol 2014;133:751-758

SLIT Ragweed Outcome: Total Combined Score (TCS)



Creticos PS et al *J Allergy Clin Immunol* 2014;133:751-758

SLIT,SCIT Efficacy for HDM



Calderon MA, et al J Allergy Clin Immunol Pract 2015;3:843-855

SLIT: Systematic Review

- Study: RCTs of SLIT vs comparators
  - 63 RCTs (n= 5,131)
  - Only USA-available products
  - Must have clinical outcomes reported
  - Ages 4 years-74 years included

Lin SY et al JAMA 2013;309(12):1278-1288

SLIT Systematic Review Conclusions

"The overall evidence provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the Rx of allergic rhinitis and asthma…."

Lin SY et al JAMA 2013;309(12):1278-1288

SLIT Systematic Review Safety

"There were no reported episodes of anaphylaxis, life-threatening reactions, or death in any treated patients across studies."

Lin SY et al JAMA 2013;309(12):1278-1288

Disease Modifying Effects of SLIT *Phleum pratense* (Timothy Grass)

- Study: RDBPCT rhinoconjunctivitis subjects
- Inclusion (n=257):
  - Adults18-65 years
  - ≥2 years Sx
  - Sx interfere with sleep &/or ADL despite Rx
  - + *P pretense* skin test (wheal ≥3 mm)
  - + *P pretense* IgE (Class ≥2)

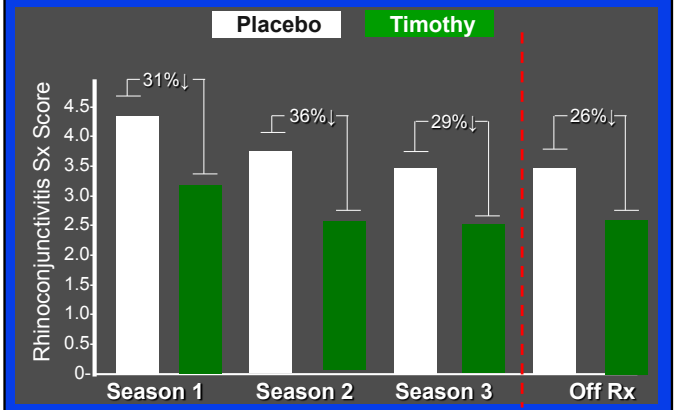
Durham SR et al *J Allergy Clin Immunol* 2010;125:131-138

Disease Modifying Effects of SLIT *Phleum pratense* (Timothy Grass)

- Rx: Timothy grass tablets SL vs placebo
  - Rx initiation 4-8 months pre-season
  - Rescue: as per pt preference (desloratidine 5 mg/d, olopatadine (1 mg/ml) 1 gtt b.i.d., budesonide NS (32 mcg/inh) 2 puffs b.i.d., prednisone 5 mg (≤60 mg/d)
- Season: 1st 3 days with grass pollen ≥10grains/m^3 thru last 3 days of 10 grains/m^3
- Outcome: Sx and Med Scores

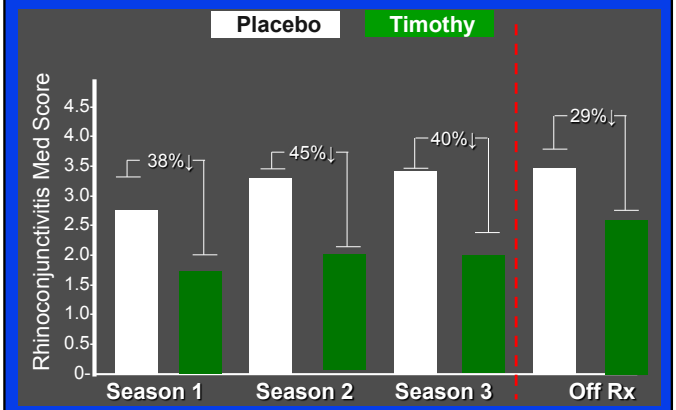
Durham SR et al *J Allergy Clin Immunol* 2010;125:131-138

Disease-Modifying Effects of SLIT: Sx *Phleum pratense* (Timothy Grass)



Durham SR et al *J Allergy Clin Immunol* 2010;125:131-138

Disease-Modifying Effects of SLIT: Meds *Phleum pratense* (Timothy Grass)



Durham SR et al *J Allergy Clin Immunol* 2010;125:131-138

Disease-Modifying Effects of SLIT

"In conclusion, the sustained, statistically significant, and clinically relevant efficacy of the grass AIT during the follow-up season establishes disease modification, the one distinct feature separating allergen-specific immunotherapy from all other treatment options for allergy."

Durham SR et al *J Allergy Clin Immunol* 2010;125:131-138

SLIT Timothy Grass: Inclusion

- Adults age 18-65 years
- Hx grass-induced allergic rhinoconjunctivitis X ≥2 years
  - Interferes with ADL or sleep
  - Bothersome despite Rx
  - + prick test and IgE class ≥ 2

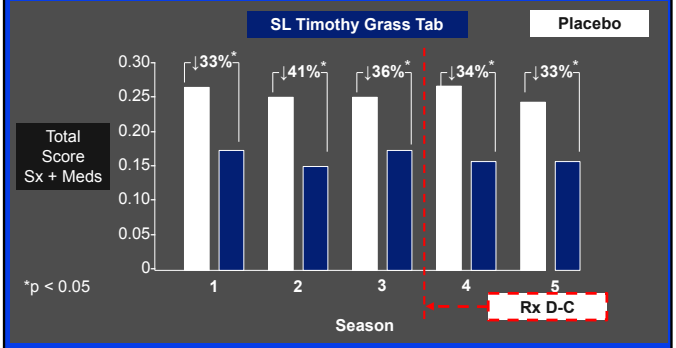
Durham SR et al *J Allergy Clin Immunol* 2012;129:717-25

SLIT Timothy Grass: Exclusions

- Fev1 < 70% predicted
- Sensitive to other allergens overlapping timothy grass pollen season
- Perennial rhinitis (e.g. house dust)
- Hx of angioedema or anaphylaxis

Durham SR et al *J Allergy Clin Immunol* 2012;129:717-25

SLIT: Timothy Grass Tablets



Durham SR et al *J Allergy Clin Immunol* 2012;129:717-25

Timothy Grass SLIT: Safety

	Timothy Grass Extract	Placebo
Oral pruritus	44%	4%
Mouth edema	19%	1%
Throat irritation	13%	2%
Ear pruritus	12%	1%

"…onset was typically on the 1st or 2nd day….duration was short (typically for 5-10 minutes after tablet intake for 2-8 weeks)."

Durham SR et al *J Allergy Clin Immunol* 2012;129:717-25

Timothy Grass SLIT: Safety

"No safety issues in relation to the trial Rx were reported. However, the Rx did cause local application site-related adverse events."

Durham SR et al *J Allergy Clin Immunol* 2012;129:717-25

Immunotherapy Payoff:
↓ Likelihood of Asthma/New Allergic Sensitizations

"…immunotherapy for allergic rhinitis may reduce the risk for later development of asthma…."

Juggins JL et al "Allergen Immunotherapy" *Am Fam Phys* 2004;70:689-696

Immunotherapy Payoff:
↓ Likelihood of Asthma/New Allergic Sensitizations

…. early Rx with allergen immunotherapy in children who were sensitive only to house dust mites reduced development of sensitivity to other allergens."

Juggins JL et al "Allergen Immunotherapy" *Am Fam Phys* 2004;70:689-696

Immunotherapy Reduces Future Sensitivity to New Allergens

- Study: asthmatic children (age 2-6 years) sensitized only to house dust mite (n = 44)
- Rx: House dust mite desensitization vs no intervention X 3 years
- Outcome: Incident new allergen sensitivity

Des Roches A et al *J Allergy Clin Immunol* 1997;99:450-453

Immunotherapy Reduces Future Sensitivity to New Allergens

Asthmatic Monosensitive	**% with new allergen sensitivities at 3 years**
House Dust Desensitized	55%*
Control	100%

*p = 0.001

Des Roches A et al J Allergy Clin Immunol 1997;99:450-453

What did the Kids Become Newly Sensitized To?

	% with new allergen sensitivities at 3 years
Cat Dander	53%
Dog Dander	35%
Alternaria	24%
Pollen	20%

Des Roches A et al J Allergy Clin Immunol 1997;99:450-453

SLIT Systematic Review Conclusions

"The overall evidence provides a moderate grade level of evidence to support the effectiveness of sublingual immunotherapy for the Rx of allergic rhinitis and asthma…."

Lin SY et al JAMA 2013;309(12):1278-1288

Immunotherapy for Asthma & Allergic Rhinitis Allergy Shots (SCIT) or Sublingual (SLIT)?

"…a growing body of evidence from DBPC studies shows that both SLIT and SCIT are effective in reducing Sx scores and medication use, improving QOL, and inducing favorable changes in specific immunologic markers."

Jutel M "Allergen-Specific Immunotherapy in Asthma"
Curr Treatment Options in Allergy 2014;1:213-219

Allergy Shots (SCIT) or Sublingual (SLIT) **So Which is Better?**

"Due to the very limited evidence from head-to-head comparative studies and variability of the end-point used in different studies, it is currently not possible to assess superiority of either route of vaccine administration."

Jutel M "Allergen-Specific Immunotherapy in Asthma"
Curr Treatment Options in Allergy 2014;1:213-219

'Traditional' Immunotherapy (SCIT) Safety Deaths from Anaphylaxis

- USA (42 yrs data): 46 deaths
  - Mistaken dose in 1/3 cases
- England (18 yrs data): 5 deaths
  - Less-experienced clinician in most cases

But What's the DENOMINATOR?

Norman PS *J Allergy Clin Immunol* 1989;84(4)Part 1:438-439

SCIT Safety

"One estimate of allergen usage, based on annual studies from a panel of 2,000 physicians in the US, indicates that in each of the previous 5 years, seven -10 million allergen injections had been administered."

46 deaths/420 million injections = **±1 death/10 million injections**

Lockey RF et al "Fatalities from Immunotherapy and Skin Testing" *J Allergy Clin Immunol* 1987;79:660-677

Traditional Immunotherapy (SCIT) Safety: Systemic Reactions

"…the percentage of systemic reactions is low; ~0.2%"

Calderon MA, et al J Allergy Clin Immunol Pract 2015;3:843-855

SLIT Serious Systemic Reactions (Anaphylaxis)

"One recent review documented 11 reported cases of nonfatal anaphylaxis, per the WAO criteria, out of 1 billion SLIT doses given since 2000."

Jamers C, Bernstein DI "Allergen immunotherapy: an updated review of safety" *Curr Opin Allergy Clin Immunol* 2017;17(1)Feb:55-59

SLIT Systematic Review Safety

"There were no reported episodes of anaphylaxis, life-threatening reactions, or death in any treated patients across studies."

Lin SY et al JAMA 2013;309(12):1278-1288

PREMERA BLUE CROSS

MEDICAL POLICY – 2.01.17

Sublingual Immunotherapy as a Technique of Allergen-Specific Therapy

BCBSA Ref Policy: 2.01.17

Effective Date:	Dec. 1, 2017	RELATED MEDICAL POLICIES:
Last Revised:	Nov. 9, 2017	2.01.500 Allergy Testing
Replaces:	N/A	

SLIT Coding

CODE	DESCRIPTION
CPT	
95199	Unlisted allergy/clinical immunologic service or procedure

Blue Cross Medical Policy 2.01.17
(effective 12/1/17)

Allergy Shots (SCIT) or Sublingual (SLIT) **So Which is Better?**

"Due to the very limited evidence from head-to-head comparative studies and variability of the end-point used in different studies, it is currently not possible to assess superiority of either route of vaccine administration."

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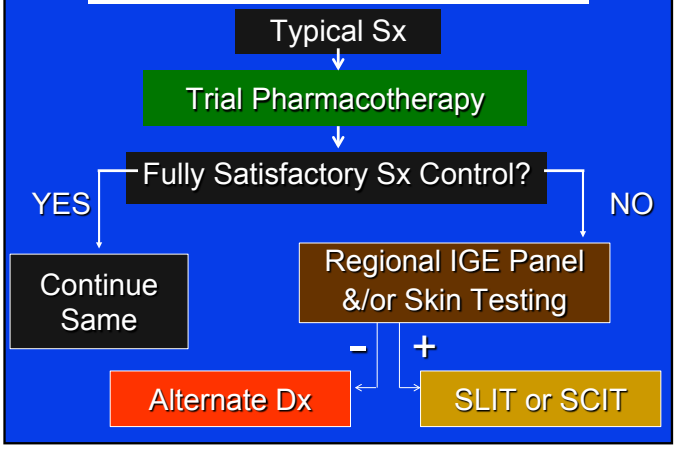
Allergic Rhinoconjunctivitis



ARC Conclusions

- ARC is common and consequential
- Pharmacotherapy is the 'traditional path'
- Despite good pharmacotherapy many patients remained dissatisfied
- SLIT/SCIT are the only disease-modifying treatments for ARC
- SLIT is safe and readily employed in the primary care setting

SELF EVALUATION

New Treatment Options for Allergic Rhinitis

1. Your patient reports PERENNIAL ARC. Which allergen below is most likely to be the culprit?

a. House dust mite (D pteronyssinus or D farina)
b. Timothy grass
c. Sweet vernal grass
d. Ragweed pollen

2. Your patient reports SEASONAL ARC. Which allergen below is most likely to be the culprit?

a. House dust mite (D pteronyssinus and/or D farinae)
b. Aspergillus mold
c. Cat dander
d. Ragweed pollen

3. Your patient reports VASOMOTOR rhinitis. Which agent below is the most likely trigger?

a. Cigarette smoke
b. Johnson grass
c. Timothy grass
d. Ragweed pollen

4. Guidelines from the American Academy of Otolaryngology (2015) suggest that the diagnosis of ARC

a. Should be confirmed with CT of the sinuses
b. Should be confirmed with nasal biopsy
c. Should be routinely referred to an expert in allergy
d. Does not require imaging if consistent symptoms and signs are present

5. The neurologic system primarily responsible for mediating rhinorrhea and post nasal drip is

a. Cholinergic
b. Histaminergic
c. Dopaminergic
d. Adrenergic

6. For ARC sufferers, which allergen has been successfully treated with SUBLINGUAL immunotherapy

a. House dust
b. Penicillin
c. Cat dander
d. IV contrast dye

7. There are more than 30 states in which an auto accident can be classified as DUI if the patient is taking

a. Loratadine (e.g. Claritin)
b. Fexofenadine (e.g., Allergra)
c. Cetirizine (e.g. Zyrtec)
d. Ozymetazoline (e.g. Afrin)

Answer Key: 1. A, 2. D, 3. A, 4. D, 5. A, 6. A, 7. C

Ralph F. Valitutti, Esq.

Ralph F. Valitutti, Esq., of Detroit, Michigan, is a senior partner at Kitch Drutchas Wagner Valitutti & Sherbrook where he heads the firm's catastrophic injury division and serves as national counsel for insurers, excess insurers, and major health systems in catastrophic injury cases. In more than four decades as a trial lawyer, Mr. Valitutti has tried more than 70 significant trials involving complex issues.

Since 2007, Mr. Valitutti has pioneered efforts to identify and correctly present actual (as opposed to claimed) costs of future care in injury cases. Mr. Valitutti is AV Peer Review Rated 5/5, was recognized by the American International Group (AIG) as one of the company's top 10 trial lawyers. In 2016, he received the Michigan Defense Trial Counsel award for Excellence in Defense.

You may contact Mr. Valitutti with your questions and comments at (586) 493-4431, or by email at Ralph.Valitutti@kitch.com.

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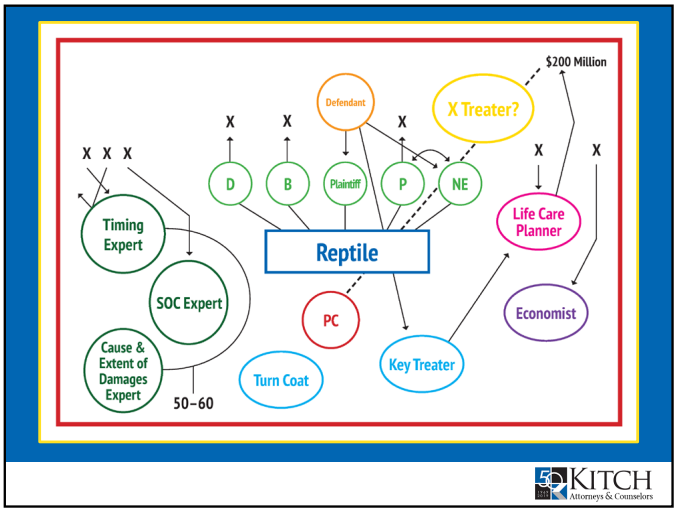
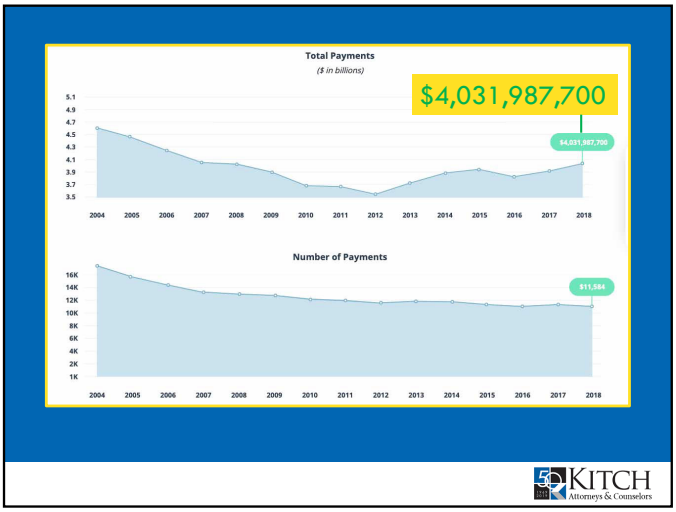
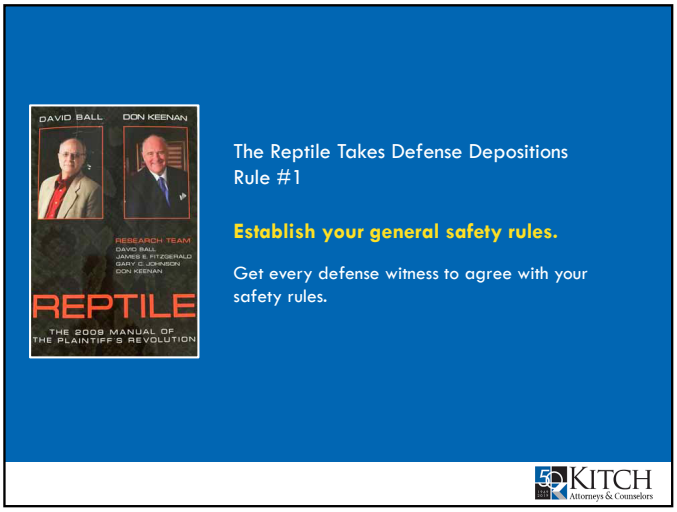
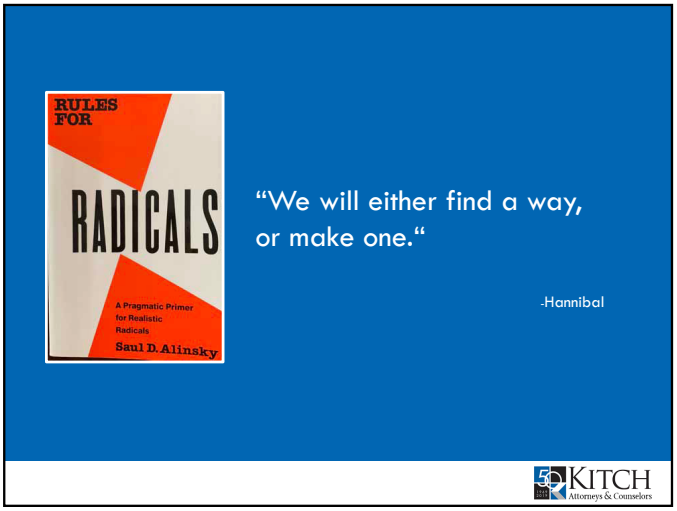
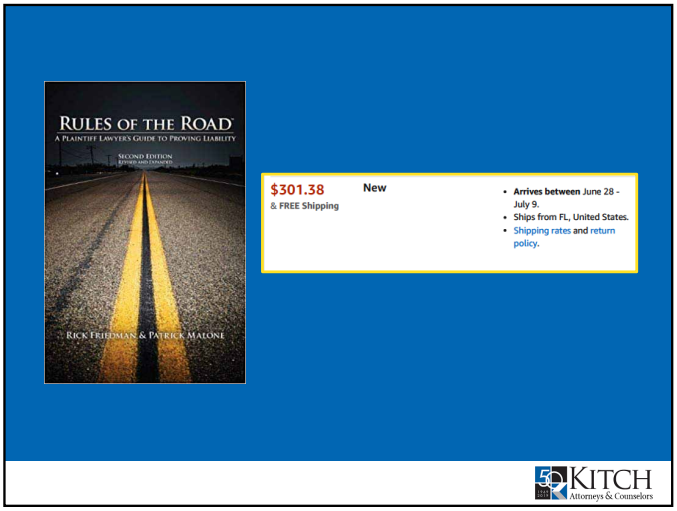
Defendant Doctor's Deposition: "The New Trial"











Rules From Reptile	10 Rules
1. Never Separate a rule from the danger	1. Never speak over the experience of your people
2. Protect the jury from harm	2. Make the enemy live up to their own book of rules (you can kill them with this.)
3. Rule gathering – use the rules of the defendant against them	3. Power is not only what you have but what the enemy thinks you have
4. Where there is no rule, make one up and press it. Keep up the pressure. Never use language the defendant is familiar with.	4. Wherever possible go outside of the experience of the enemy
5. Use terminology that is not part of the standard of care nomenclature.	5. Ridicule is man's most potent weapon
6. Use ridicule	6. The Threat is usually more terrifying than the thing itself
7. Safety is a behavioral imperative that supersedes all other considerations	7. If you push a negative hard enough it will break through to its counter-side
8. Make the defendant sorry for their conduct	8. Keep the pressure on
9. Show the defendant to be uncaring	9. Use language you enjoy using
10. Establish that the defendant learned nothing	10. Move to a new topic often

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KITCH Attorneys & Counselors

Chapter 5: Let the Other Lawyer Take Depositions First

Chapter 12: Ignore the Rules of Evidence and Routine Objections by Counsel

Chapter 18: Have a Deposition Misconduct Toolkit Handy

Chapter 22: Never Take a Non-Answer for an Answer

Chapter 24: Use Witness-Friendly Hypothetical Scenarios to Find More Evidence
Chapter 25: Don't Let Purported Memory Failures Go Unexplored
Chapter 26: Explore the unusually Perfect Memory

Chapter 28: Create Powerful Exhibits from Existing Evidence for Use in Depositions

Chapter 32: Summarize and Cap Witness Testimony
Chapter 33: Don't Hold Back Bombshells

KITCH Attorneys & Counselors

WHAT IS GOING ON DURING YOUR DEPOSITION

- Rule gathering
- Relating general safety rules to specific dangers
- Attempts to relate the condition of the plaintiff to violations of simple rules
- Safety rules not medical judgment should always govern your actions
- Establish that you did not care about this person
- Establish that the defendant did not know about the person's outcome
- Establish that defendant learned nothing from this experience
- Establish that defendant did not have sufficient training or experience to do the job
- Try to establish inconsistency between the defendant's written record and oral testimony, or inconsistencies between one defendant to another, or to phrases in published texts
- Show that the defendant did not document what is said at deposition
- Establish that plaintiff acted reasonably

WHAT IS GOING ON DURING YOUR DEPOSITION

Rule Gathering

KITCH Attorneys & Counselors

WHAT IS GOING ON DURING YOUR DEPOSITION

Relating general safety rules to specific dangers

KITCH Attorneys & Counselors

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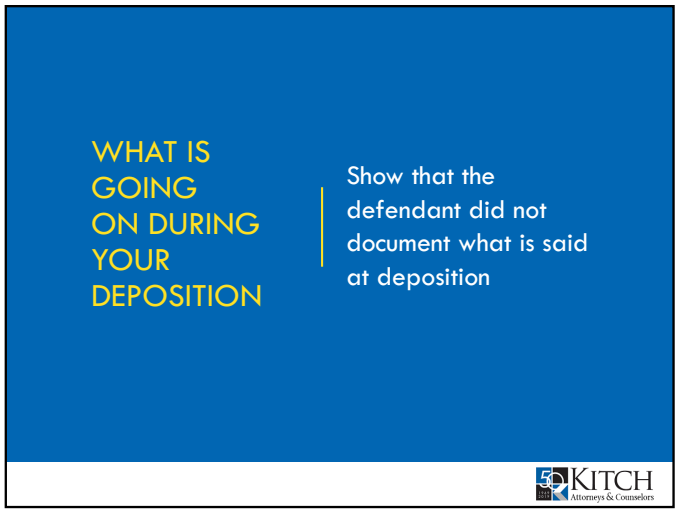

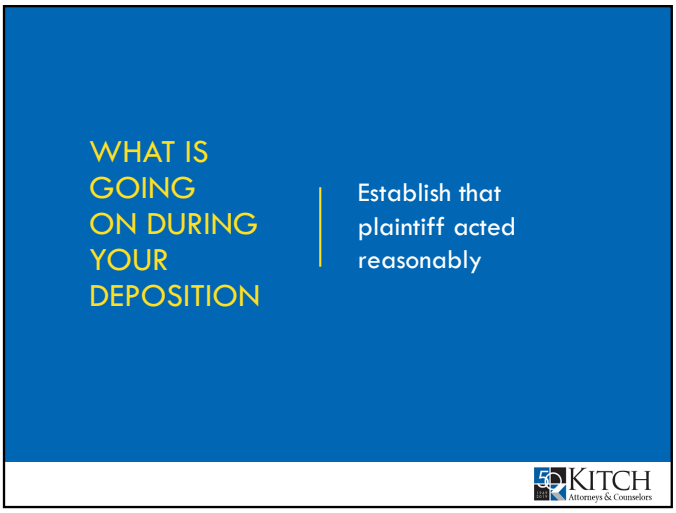

SELF EVALUATION

Defendant Doctor's Deposition: "The New Trial"

1. T/F - During the deposition of a defendant doctor, only questions allowed by the Rules of Evidence can be asked.
2. In preparation for your discovery deposition, you should set aside at least:
    a. One hour before deposition;
    b. One hour a week before the deposition;
    c. One hour a month before the deposition;
    d. All of the above.
3. T/F - Before your deposition, you should read all of the literature that is relevant to the issues in your case including your own college or academies' publications.
4. T/F - Hospital rules and regulations set forth the standard of care for physicians working in hospitals, and can help you defend your case.
5. T/F - It is a violation of a safety rule to exercise your judgment negligently.
6. T/F - If you didn't chart something, it didn't occur.
7. T/F - You do not need consent to follow patient's safety rules.
8. T/F - When you do not follow patient safety rules, you are needlessly endangering a patient.
9. T/F - Your deposition is your opportunity to win your case.
10. T/F - Before your deposition, you need to memorize the medical record.

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

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Medical Emergencies in the Healthcare Office: The Response Kit and Its Usage

Note: placing the drugs where you want them with color coding, is in itself, a practice drill for the actual emergency

Drugs included in the "Top 10 List": how delivered

- IV: 15 to 30 seconds NONE!
- IN: Equal to IV or up to 5 minutes up to 4 drugs in kit: (Midazolam, Glucogon, Narcan, Flumazenil)
- PUMP AEROSOL: Albuterol and Nitroglycerin 3-4 minutes

Drugs included in the "Top 10 List"

- INHALE: O_2, Nitrous, Spirits of Ammonia, Albuterol in Nebulizer
- IM: 5-10 minutes - Epi and Benadryl
- MUCOSAL ABSORPTION: Sublingual = Nitroglycerin
- PO: up to an hour: Aspirin = Chewed first, Benadryl Elixir = less time

Basic (10) Emergency Kit

- *Oxygen Tank as an and **"E" Cylinder"** with AMBU Bag
- 1) Epi: as EpiPen 2-Pak (0.3mg of 1:1,000) and Epi solution for IM use (1:1,000) = has 0.3mg in 0.3cc or 0.3ml of solution—and also **Epi Pen Junior*** = .15mg = 1/2 the dose.

33 lbs to 66 lbs. or
15 kg to 30 kg

Anaphylaxis

the sooner you deliver EPINEPHRINE
the sooner the patient will recover and survive!!

To differentiate from Severe Allergic Reaction

Criterion 1*

- Skin and/or Mucous Membranes
- Respiratory
- BP

Criterion 2*

- Skin and/or Mucous Membranes
- Respiratory
- BP
- GI

To differentiate from Severe Allergic Reaction

Criterion 3*

- In Children and Infants = > 30% reduction in Systolic BP
- Adults = SBP < 90 mm Hg. or > than 30% decrease from base line

Treatment for Anaphylaxis

- If respiratory distress-position upright
- If Cardiovascular distress (low BP) (LOC)
- Position supine —
- 100% Oxygen to start
- Epi 0.3mg of 1:1000 adult (up to 0.5mg)
- Note: dose is 0.01mg/kg up to 0.5mg. (221 lb = 100 Kg = 1.0 mg)
- dg

Meds to use

1) Epinephrine 0.3 mg to 0.5mg of a 1:1,000 solution IM
2) Albuterol Inhaler
3) Diphenhydramine 50 mg IV/IM
4) If on B-Blockers: Glucogon IM/IN 1.0 mg = Adult vs. 0.5mg

Basic (10) Emergency Kit

- 2) ***Spirits of ammonia** (crush and wave 8"- 10"*s* under nose). Only after 15-20 sec's
- 3) **Benadryl Elixir** and Benadryl 50mg/cc for IM injection and 50mg. tablets
- 4) Nitroglycerin spray (pump) or pills - dissolve under tongue
- 5) Aspirin (4 baby, 81mg. each) to be chewed then swallowed-taken after Nitro in "MONA"

Allergy = hypersensitive state caused by exposure to an Allergen, re-exposure to which causes a heightened capacity to react.

30% of American claim to be allergic to something.

Mild Allergic Reaction:

- Skin: hives, rash and edema can progress. The faster the progression occurs the worse it can become
- Must check throat and lips, sound of voice and lung sounds, while looking and listening a BP cuff is placed on the arm! CALMLY!!
- patients ability to talk is critical-engage in conversation..throughout episode...

Likely office allergins..

- Latex
- Antibiotics
- Aspirin
- Flavoring in the topical
- Acrylic liquids

DELAYED REACTION (60 minutes after exposure to allergin)

- LOCAL REACTION: Slow progression- Hives, Itching, Rash and Flushed skin This is not life threatening---treatment is PO (liquid) Benadryl 50mg. 3X day x 3 days..

VS.

- If progressing quickly-and spreading, or the patient is very uncomfortable then give IM Benadryl-50mg-(1.0 ml) into the Deltoid Muscle

- If the onset of the skin reaction is rapid- but no Respiratory or CV involvement-- treatment will be 50 mg IM Benadryl-- plus 100% O_2 and immediate taking of vital signs.....Epi-ready! The key word is "rapid"
- Rapid onset= 911, IM Benadryl / Epi ready

Nitroglycerine

SL administration = vasodilation results in a reduced venous return, or preload reduction, lowering myocardial O_2 consumption.

Blocks- Phosphodiesterase

Nitroglycerine dilates the coronary vessels of the heart by 28%

With signs of angina pectoris, one tablet or spray (0.3 or 0.4 mg) should be administered sublingually.

Relief of pain should occur within minutes. If necessary, this dose can be repeated twice more in 5-minute intervals.

Systolic blood pressures below 90 mmHg will contraindicate the use of this drug as well as use of ED meds within 24 hours.

Aspirin Thrombolytic

Aspirin: reduces mortality from acute MI @162 mg. Few contraindications. These would include known hypersensitivity to aspirin, severe asthma or history of significant gastric bleeding

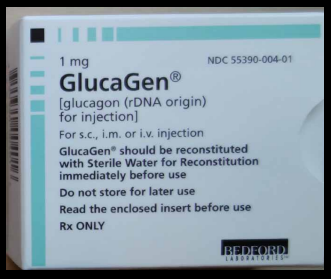
Basic (10) Emergency Kit

- 6) Albuterol (ventolin or proventil), presently Pro-Air and/or **Nebulizer with Albuteral packets**
- 7) Glucose (insta-glucose) Glutose*, Packets of sugar, soft drinks, and GlucaGen which is **Glucogon for IM/IN use—1.0mg/cc**

- 8)* **Midazolam (Versed) IM/IN use** - 5.0mg/ml for a BSS Condition - NYC -since 1978 - 15 Snow Blizzards

Treatment of Bronchospasm (Asthma)

- 1) Comfortable position-usually sitting up
- 2) 100% Oxygen
- 3) Use of inhaler (bronchodilator)-2X and consider use of a nebulizer 5 minutes of continuous albuterol flow
- 4) Call EMS if 2 doses does not relieve spasm or if there is no prior history of asthma--R/O possible Anaphylactic reaction..
- 5) If condition worsens EMS-Epi 0.3mg of 1/1000



Precose and Glyset

Glucogon

- **Glucagon is available as 1 mg formulation, which requires reconstitution with its diluent immediately prior to use**
- **One dose of Glucogon can raise your blood sugar by as much as 250mg/dl, depending on how much glycogen was stored in the liver.**
- **Side Effect of use: can be significant nausea which can be treated with 10-15 mg Reglan (Metoclopramide) as an Elixir/Oral solution for an adult.**

Glucogon

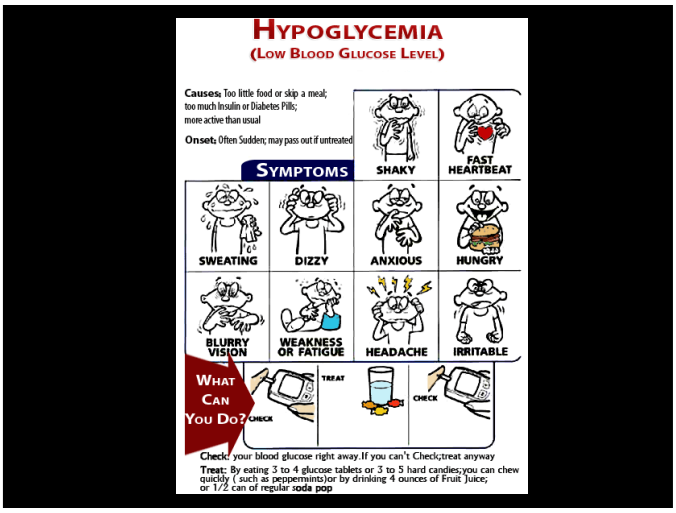
- **Glucagon is indicated if an intravenous line is not in place and venipuncture is not expected to be accomplished, as may often be the case in a dental office. If able to start an IV then 40-50 cc's of 50% Dextrose solution for an adult and 20 cc of 50% Dextrose for a child or anyone under 100 lbs. Titrate as necessary.**
- **The dose for an adult (Glucogon) is 1 mg - IM or IN. If the patient is less than 20 kg, (44 lbs) the recommended dose is 0.5 mg.**

Normal Blood Sugars

- A normal fasting (no food for eight hours) blood sugar level is between 70 and 99 mg/dL
- A normal blood sugar level two hours after eating is less than 140 mg/dL

Diabetes is diagnosed by any one of the following:

1. Two consecutive fasting blood glucose tests that are equal to or greater than 126 mg/dL
2. Any random blood glucose that is greater than 200 mg/dL
3. An A1c test that is equal to or greater than 6.5 percent. A1c is an easy blood test that gives a three month average of blood sugars
4. A two-hour oral glucose tolerance test with any value over 200 mg/dL



Signs and Symptoms of Hypoglycemia:

Shaking-tremor
Tachycardia
Sweating
confusion-disorientation
cold moist skin
cannot reason with patient
bizarre behavior to
deer in the headlights
numbness of lips, fingertips
tremors
headache
Lack of or poor coordination

8 Classes of Oral Meds for Diabetes

- **Alpha-glucosidase inhibitors:** blocks the action of alpha-glucosidase which breaks down carbs like starches and Sucrose to Glucose. *Acarbose* (***Precose***) and *Miglitol* (***Glyset***). This slows down digestion and so glucose passes into the bloodstream slowly and blood glucose levels stay lower after a meal. Side effect is abdominal discomfort from the undigested carbs. Often combined with other meds that can cause hypoglycemia ***Do not give sucrose (table sugar or candy) as it will have little effect. So give Glucose (Dextrose) as tablets or a gel..***

Precose and Glyset

Treatment for Hypoglycemia

- Sugar drinks...O.J. (usually first choice), then soft drinks (not diet), fruit juices, and candy* except when on:
- You may have to force the patient to drink this-but only while conscious!
- If patient is going to altered consciousness: do not use cake frosting in a tube or Insta-Glucose
- Can be aspirated into lungs
- If fully recovered from hypoglycemia--continue with treatment if you AND the patient are comfortable.
- Patient can go home, if they are fully recovered from hypoglycemia*
  * How does this compare to Syncope?
- If in doubt.....?

Newest additions all for IN use

Basic (10) Emergency Kit

- 9)* **Narcan:** also IN use "Up to 2mg" objective is to relieve Resp Depression.If too fast - violent and can show withdrawal with major SE's.
- 10)* **Nitrous Oxide** 4l/4l = pain relief of 10mg Morphine without Resp. Depression

#11 - Hands: Yours and your Patients

- What is the one drug you do not administer for Hyperventilation?
- Oxygen

As of 2018,
22 States require AED's in the Dental Office

#13,14 and 15 - if IV access, and/or using Oral Sedation

- IV equipment, Dextrose 50% solution
- Flumazenil (Romazicon) (up to 1.0 mg - IN)
- Lorazepam (sublingual) Ativan (3-4mg)

Syncope (fainting)

Vaso/Vagal Syncope=
transient loss of consciousness due to transient global cerebral hypoperfusion

Common Causes of Syncope: (24)

- ***Vaso-Vagal***
- ***Cerebral Hypoxia***
- ***Hypoglycemia***
- ***Anemia***

Unconsciousness continued…

associated with pain

- Subarachnoid Hemorrhage
- Aortic Dissection
- Abdominal Aortic Aneurysm
- Pulmonary Embolism
- Ectopic Rupture

Loss of consciousness..

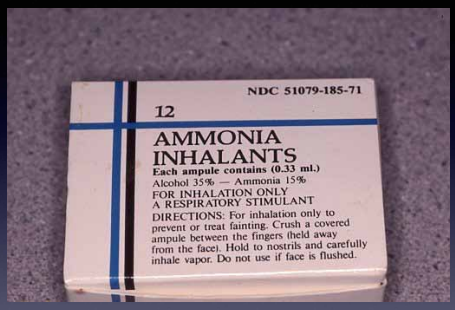
- lack of response to sensory stimuli

S.O.S.

- Supine-HT/CL
- Oxygen
- Spirits of Ammonia

Position

- This is often the only treatment necessary for complete recovery
- Syncope = Supine--Head Tilt/Chin Lift
- When not managed correctly this can be the only reason for a fatal outcome
- S



- Use of Ammonia Inhalants creates a child's response to fear.....

Definitive Treatment- SYNCOPE SOSSOS

- Position: SUPINE
- Head/Tilt and Chin/Lift
- place Oxygen on face or nose, continue Head/Tilt and Chin/Lift...
- If no response within 15 to 20 seconds...
- Spirits of ammonia- crush and wave under nose
- cold compress to forehead
- If at 20-30sec's-and Hx of Diabetes-Sugar-(911) BS Test-Glucogon if BSS
- Next rule/out=Cardio-vascular—(911)—Oxygen--Supine or Upright - AED ready
- Vital signs-Stabilize

SOSSOS

- Supine
- Oxygen
- Spirits of ammonia
- SUGAR
- Oxygen
- Stabilize

- If Loss of Consciousness is > 15 - 20 seconds then ...
- Spirits of Ammonia - if some (mild) response then consider:
- HYPOGLYCEMIA followed by an ARRHYTHMIA, DEHYDRATON, ANEMIA, UTI, STROKE, A.I.

Stroke Assessment

- Cincinnati Stroke Scale...used in ER
- Simple scale for office use...(FAST)
- F) Facial Drooping
- A) Arm drift
- S) Slurred Speech
- T) Time is CRITICAL = call 911!! FAST

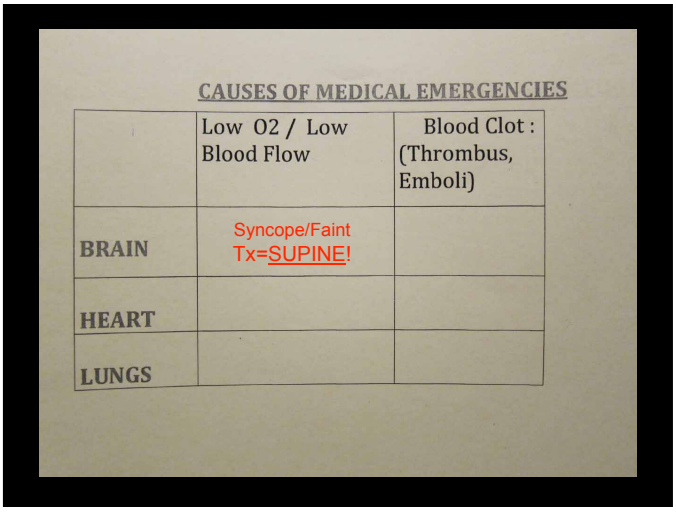
(If one of the 3 = 72% Stroke, if all 3 present = 85% Stroke)

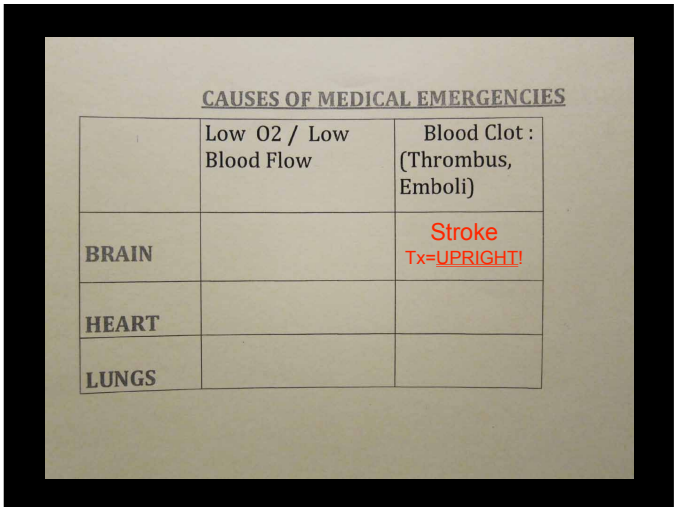
Treatment for a Stroke=CVA

- Call 911 (as a post it-code-126)
- Oxygen and upright, semi-fowlers (not supine!)--also to prevent aspiration
- 80% = clot/occlusive/ischemic
- up to 20% = Hemorrhagic No aspirin* Pt may indicate severe headache

Syncope and Stroke LOCATION is everything

- With these two medical emergencies-- POSITION is everything!
- If there is no breathing or Pulse?=UNRESPONSIVE=R/O Cardiac Arrest then....911-CPR-AED
- ACTIVATE EMS 911





Causes of Seizures

*Hypoglycemia (Diabetes)
*Cerebral Hypoxia
*Local Overdose
*Stroke
Head injuries
High Temperature
Meningitis
Brain tumor
Hyperthyroidism
Electrolyte imbalance
Drugs/alcohol
Renal failure
Toxins

Causes of Seizures:

- Stress - Epileptic history, low seizure threshold (new environment, new people)
- Cerebral Hypoxia (Iatrogenically induced)... from syncope + inadequate airway = not placing patient supine and not performing Head/Tilt, Chin/lift-(eg. allowing patient to dictate protocol)

Causes of Seizures

not from Epilepsy..

- Cerebral Hypoxia
- Hypoglycemia-if untreated - Glucogon-BSS
- Local Anesthetic Overdose-shaking after local administration - Mild

Simple suggestions to avoid most Emergencies…

- Take a BP on everyone
- Give supplemental Oxygen when indicated
- D_A_S_H_ EP/ET = Every pt / every time
- Use a Pulse Oximeter for Oxygen Saturation, Pulse (RPP)

SELF EVALUATION

Medical Emergencies in the Healthcare Office: The Response Kit and Its Usage

1. A diabetic patient has Altered Consciousness and is taking Precose (Acrarbose) as one of their medications. What should you administer?

a. Orange juice
b. Candy
c. Soda (non-diet)
d. Glucose Gel

2. The most important drug in the Emergency kit is:

a. Oxygen
b. Epi
c. Benadryl
d. Albuterol
e. Glucagon
f. Ammonia inhalants

3. Some common side effects of administering Epinephrine can be:

a. Hypertension
b. Tachycardia
c. Angina
d. Congestive Heart Failure
e. All of the above

4. T/F - Nitrous Oxide can be administrated during a Myocardial Infarction

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

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Screening for and Treating Hepatitis C

Hep C: Definition

- "Hepatitis C is an acute liver parencyhymal infection caused by hepatitis C virus."
- Synonyms: "Transfusion-related non-A, non-B hepatitis"

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Hep C: Why Bother?

"Hepatitis C infection is the most common chronic blood-borne infection in the US. About 3% of baby boomers test positive for the virus."

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Hep C: USA Demographics

- Prevalence:
  - HCV ab+: 1%-2% (n=2.7 million)
  - Hemophiliacs transfused <1987: 72%-90%
  - Injection Drug Use: 72-90%

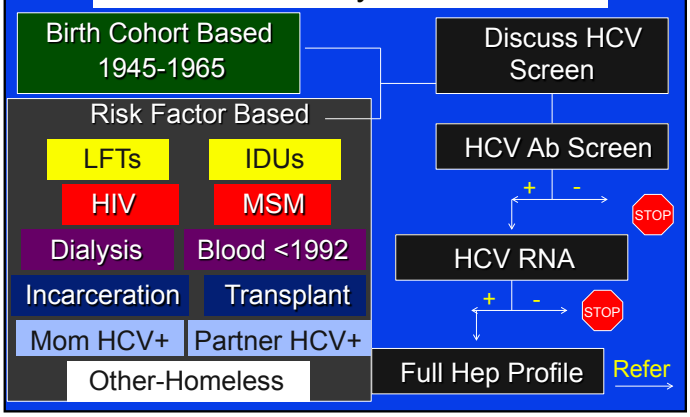
Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Hep C: A Place of Embarcation

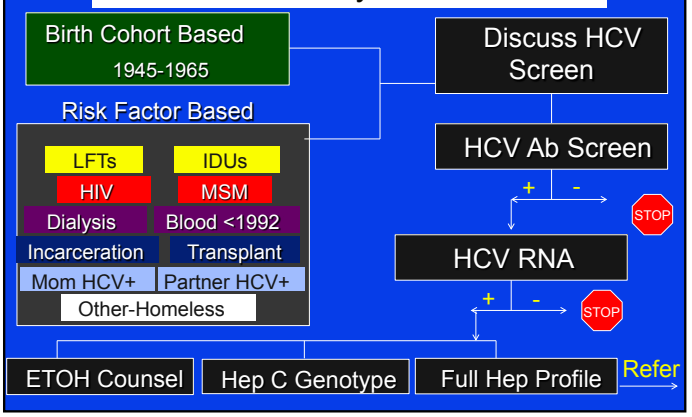
"Only 20 years after the discovery of the Hepatitis C virus, a cure is now likely for most people affected by this chronic infection, which carries a substantial disease burden, not only in the United States but also worldwide."

Liang TJ, Ghany MG NEJM 2013.368:1907-17

HCV: Primary Care Role



HCV: Primary Care Role



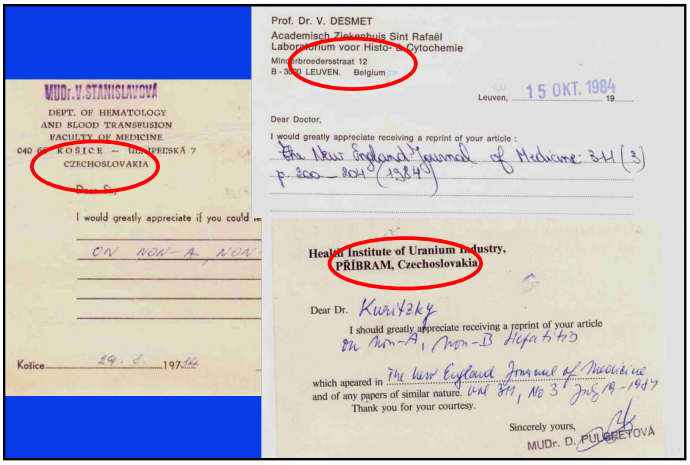
July 19, 1984

JOURNAL OF MEDICINE July 19, 1984

ON NON-A,NON-B HEPATITIS

To the Editor: Why can't we just call it hepatitis C?

Louis Kuritzky, M.D.
Alachua General Hospital
Gainesville, FL 32602



HCV: A Compelling Epidemiologic Presence

"About 3 million Americans are thought to have hepatitis C, but because the disorder can be aSx for years, only a quarter know that they are infected."

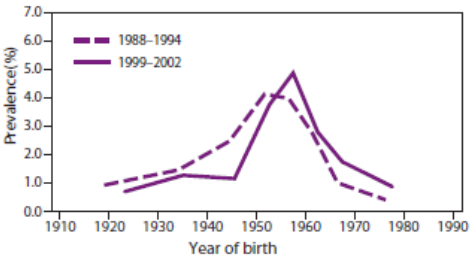
Lancet 2013;381(May 18):1688-1688

HCV Prevalence NHANES 1998-2008

HCV ab+	n
1.5%	3.9 milliion
+ Homeless + Incarcerated	0.5-1 million
TOTAL	4.5-4.9 million

MMWR 2012;61(4):1-36

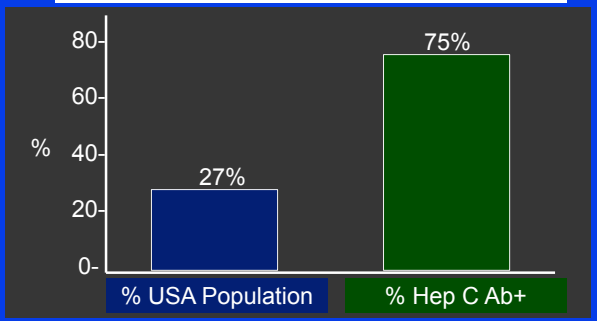
NHANES: Hep C Prevalence



Source: Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Internal Med 2006;144:705–14. Modified and reprinted with permission from Annals of Internal Medicine.

MMWR 2012;61(4):1-36

Birth Cohort 1945-1965 Disproportionate Hep C Burden



MMWR 2012;61(4):1-36

Who Should Be Hep C Screened?
Age-Independent At-risk Groups

Abnormal LFTs
HIV+
EVER Illicit Parenteral Drug User
Health-care exposures
EVER Chronic hemodialysis
Clotting Factor Concentrates <1987
Organ transplant recipient <1992
Transfusion recipient <1992
Transfusion recipient HepC + donor
Children of HepC + Mother

MMWR 2012;61(4):1-36

Transfusion Risk pre-1992 vs Now

"In the US, advances in screening of blood and blood products have made transfusion-related HCV infection rare (the risk is estimated to be 0.001% per unit transfused)."

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Clinician Hep C Risk: Needle-Stick Exposure

"Occupational needlestick exposure from an HCV-positive source has a seroconversion rate of 1.8% (range 0%-7%)"

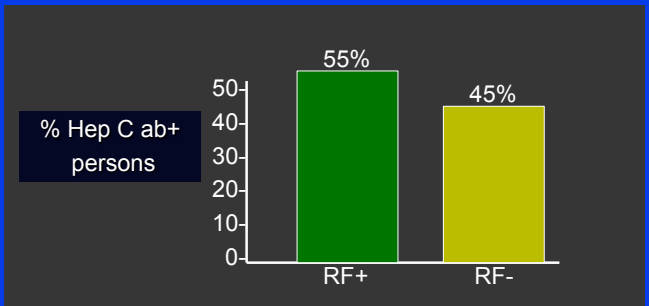
Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Why the Change from CDC-Recommended Risk Factor Based Screening (1998)?

"Many persons with HCV infection do not recall or report having any of these specific risk factors."

MMWR 2012;61(4):1-36

Risk-Factor Based Screening: Good Enough? CDC Data 2012



MMWR 2012;61(4):1-36

Hep C: Clinical Scenario

- Most cases (70-80%) subclinical
- If symptomatic
  - Sx usually begin 7-8 wks post-infection
  - 2-26 wks range
- Acute Sx (10-20%): jaundice, abd pain, anorexia malaise
- Chronic HCV: 60-70% Persistent or fluctuating LFTs (30-40% normal LFTs)

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Hepatitis C Natural Hx

Hep C ab+ persons

↓ 20 yrs

20% Cirrhosis

↓

Death from HCV-related Cause

MMWR 2012;61(4):1-36

Hep C: Long-Term Outcomes (Untreated)

Acute Hepatitis C

↓ 55%-89%

Chronic Hep C

↓ 2-24% over 20 years

Cirrhosis

3%/yr ↓ Hepatic Decompensation

1-4%/yr ↓ Hepatocellular Carcinoma

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Hep C: *Some* Extra-Hepatic Sequelae

Cryoglobulinemia
Membranoproliferative Glomerulonephritis
Sjogren's sydrome
Autoimmune thyroiditis
Polyarteritis nodosa
Lichen Planus
Bcell lymphoma
Porphyria cutanea tarda

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Since Most Folks Don't Know WHEN They Acquired HCV….

Marker	Mean Post-Transfusion Span
Mild Chronic Hepatitis	13.7 years
Severe Chronic Hepatitis	18.4 years
Cirrhosis	20.6 years
HCC	28.3 years

Bisceglie AM Hepatology 2000;31(4):1014-1018

HCC
Hepatocellular Carcinoma

- 3rd Leading CA Mortality worldwide
- Increased USA incidence
  - ↑NAFLD
  - ↑ HCV
- Survival
  - Early stage: 5yr = ±70%
  - Advanced stage: < 1yr

Singal AG, et al JNCCN 2014;12(3):375-382

HCC: Surveillance

- Cirrhosis: Ultrasound Q6m
- US sensitivity for early stage: 32%
- 4-phase CT or MRI for abnormal US
- 40% HCC patients present with no previously recognized liver disease

Singal AG, et al JNCCN 2014;12(3):375-382

Natural Hx of Hepatitis C
Factors with NEGATIVE Impact

- Alcohol
- Hepatitis B
- HIV
- MSM
- HLA Type B54
- Male Gender
- Age of Onset

Di Bisceglie A Hepatology 2000;31(4):1014-1018
Hosein SR, Wilson DP Lancet 2013;382 (Sept 28):1095-1096

Cirrhosis RF Stratification in Chronic Hep C

Risk Factor	Relative Impact
Alcohol Use	++++
HIV	++++
HBV	+++
BMI	++
Age	++++
Duration of HCV infection	+++
HLA B54	+ (?)

adapted from Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

The HIV:HCV Connection
Data from New South Wales, Australia

"…13.1% of people with HIV are co-infected with HCV and 38% of MSM report using recreational drugs in the past 6 months."

Hosein SR, Wilson DP Lancet 2013;382 (Sept 28):1095-1096

What to do about Children Born to HCV Infected Mom

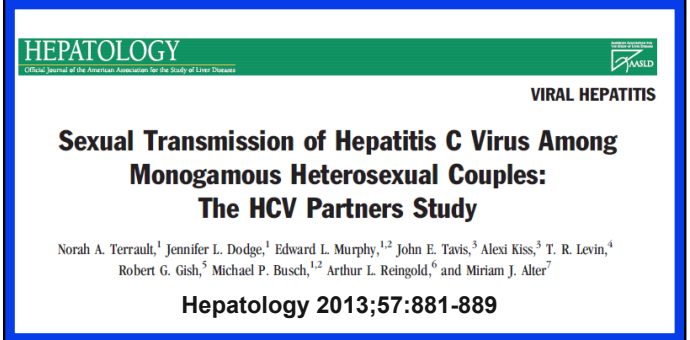
- Vertical transmission low (5-6%)
- Check antibody after age 1 yr
  - Confounding maternal antibody
  - Infants have very high clearance level

Kuritzky L Keeffe EB Fam Pract Recert 2006;28(2):41-57

HCV Sexual Transmission

- Monogamous partner rate ±1.5%
- Risk increased with multiple partners
- HIV increases risk

Kuritzky L, Keeffe EB Fam Pract Recert 2006;28(2):41-57


HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

VIRAL HEPATITIS

Sexual Transmission of Hepatitis C Virus Among Monogamous Heterosexual Couples: The HCV Partners Study

Norah A. Terrault,[1] Jennifer L. Dodge,[1] Edward L. Murphy,[1,2] John E. Tavis,[3] Alexi Kiss,[3] T. R. Levin,[4] Robert G. Gish,[5] Michael P. Busch,[1,2] Arthur L. Reingold,[6] and Miriam J. Alter[7]

Hepatology 2013;57:881-889

Sexual Transmission of Hep C
500 Sero-discordant Couples
F/u 15 years (median)

"Based upon 8,377 person-years of follow-up, the maximum incidence rate of HCV transmission by sex was 0.07% per year, or approximately one per 190,000 sexual contacts."

Terault NR, et al Hepatology 2013;57:881-889

If the Patient Had Chronic Hep C, Wouldn't LFT's be Up?

"…about 30% of patients with HCV infection do not have elevated ALT levels."

Kuritzky L Keeffe EB Fam Pract Recert 2006;28(2):41-57

Well, At Least If the LFTs Aren't Up, No Liver Damage is Happening, Right?

"Absence of elevated ALT levels is in no way 'protective'; persons with normal ALT values can still progress (if they are infected with HCV) to end-stage liver disease."

Kuritzky L Keeffe EB Fam Pract Recert 2006;28(2):41-57

Does Hep C Screening Meet Public Health Testing Criteria?

Criterion	Y/N
Affects a large # of persons	YES
Causes negative heath outcomes	YES
Can be Dx before becoming Sx	YES
HCV tests readily available	YES
HCV tests minimally invasive	YES
HCV tests reliable	YES
Disease progression can be limited by Rx	YES
Life-saving	YES
Testing is cost-effective	YES

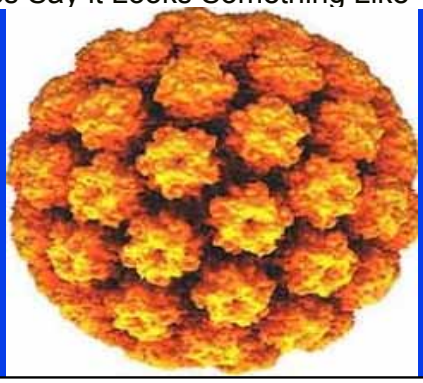
MMWR 2012;61(4):1-36

When Clinicians Detect HCV Ab, Problem Solved?

"Nearly half of Americans who test positive for HCV infection with an initial antibody test do not receive the follow-up RNA testing that is necessary to show whether they have recovered or have an ongoing infection."

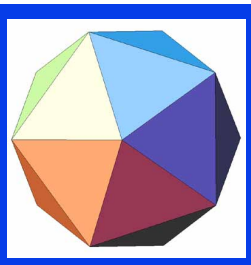
Lancet 2013;381(May 18):1688-1688

HCV Is TOO SMALL for Me to See, But Most Articles Say it Looks Something Like This…



But then, when I went to look at the Literature, researchers say it is an ICOSAHEDRAL virus, which means it looks like this:

Icosahedron
= 20 sided



Google Images: Http://pretendy.tumblr.com/post/21166239706
Accessed May 3, 2013

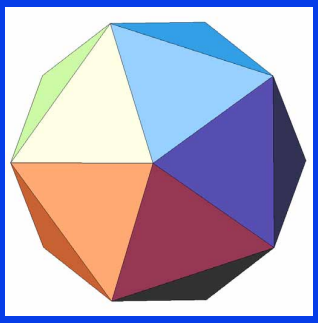
At this SAME WEBSITE, Andrew Balin, a physics student at University of Warwick, UK, says:

"… an icosahedron is the optimum way of assembling a closed shell out of identical subunits. A virus is constructed in just this way – identical triangular units called capsomers arrange themselves to form a protective closed shell around the virus genetic material. And they do this in the most mathematically optimum way, as if they've studied calculus."

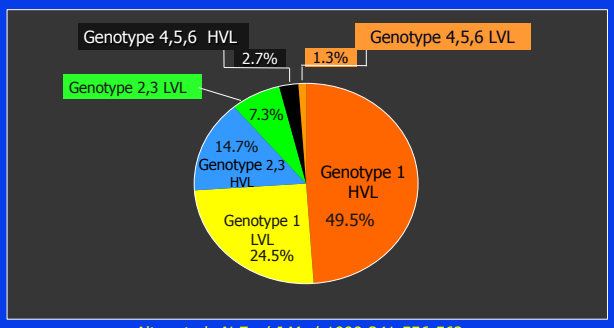
Http://pretendy.tumblr.com/post/21166239706
Accessed May 3, 2013

Icosahedral Viruses

- HPV
- Herpes Simplex
- Poliovirus
- Rhinovirus
- Hepatitis A,B,C,E
- Adenovirus
- Rubella



Genotype and Viral Load: USA



Alter et al. *N Engl J Med.* 1999;341;556-562.
Blatt et al. *J Viral Hepatitis.* 2000;7:196-202.

Why Are Evolving Rxs So Important?

- Efficacy
- Tolerability
- Ease of Administration

Sustained Viral Response: Before 2011

- Peg-Interferon Weekly + Ribavirin Daily
  - Genotype 1 SVR=40%
    48 week treatment
    Wt-based ribavirin
  - Genotypes 2,3 SVR=80%
    24 week treatment
    Low dose ribavirin (800 mg)

Side Effects of Interferon

- Flu-like symptoms
  - Headache
  - Fatigue or asthenia
  - Myalgia, arthralgia
  - Fever, chills
- Neuropsychiatric disorders
  - Depression
  - Mood lability
- Alopecia
- Thyroiditis
- Nausea
- Diarrhea
- Injection-site reaction
- Lab alterations
  - Neutropenia
  - Anemia
  - Thrombocytopenia

Side Effects of Ribavirin

- Hemolytic anemia
- Teratogenicity
- Cough and dyspnea
- Rash and pruritus
- Insomnia
- Anorexia

Interferon: Depression

- Overall mean incidence = 28%
- May be Rx-limiting adverse effect
- Associated with lack of adherence
- Begins early, peaks 4-16 weeks
- MOA
  - CNS proinflammatory cytokine activation
  - Altered CNS apoptosis
  - Altered neurotransmission
  - Similar finding in endogenous depression

Udina M J Clin Psych 2012;73(8):1128-1138

SVR: 2nd & 3rd Generation Rx

- SVR 80-90% and better
- Benefits irrespective of genotype
- Benefits consistent at all disease stages
- Reversal of fibrosis
- Simpler Regimens
- Some regimens all-oral
- Much better tolerability

Patient-Important Outcomes Critical for Decision Making

- All-cause Mortality
- Hepatocellular Carcinoma
- Sustained Virologic Response
- Rx-related Serious Adverse Events
- QOL
- Transmission
- Alcohol Use

MMWR 2012;61(4):1-36

SVR & All-Cause Mortality: YES

"…of 16,864 HCV-infected persons identified through the US Department of Veterans Affairs,… Rx-related SVR was associated with a reduction in risk for mortality….(RR = 0.45, CI 0.41-0.51)"

MMWR 2012;61(4):1-36

SVR & Hepatocellular Carcinoma: YES

"A meta-analysis…of 12 observational studies (n=25,752)…revealed that Rx-related SVR was associated with a reduced risk for HCC (>75%) among persons at all stages of fibrosis (RR = 0.24, CI =0.18-0.31)"

MMWR 2012;61(4):1-36

SVR & QOL: YES

"One systematic review was identified….the mean QOL associated with the SVR in the intervention group was 6.6 points higher on the SF-36……"

MMWR 2012;61(4):1-36

SVR & HCV Transmission: ??

No data from systematic reviews, metanalyses, or articles

MMWR 2012;61(4):1-36

SVR & Alcohol Use: Promising

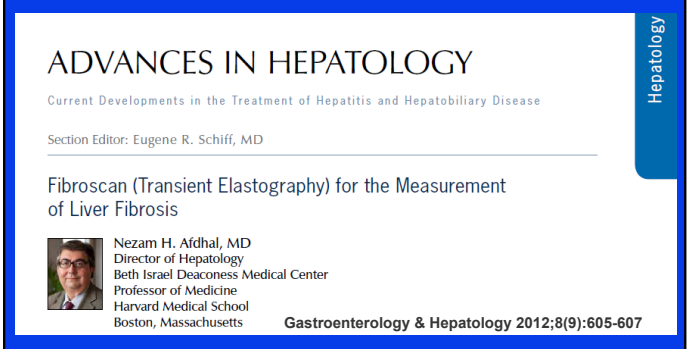
"A meta-analysis of 22 RCTs (n=7,619) examined…HCV testing followed by a brief alcohol intervention…versus testing alone. The mean reduction of drinking (g/week) was 38.4% lower than in the control groups after folllow-up at ≥1 year.

MMWR 2012;61(4):1-36

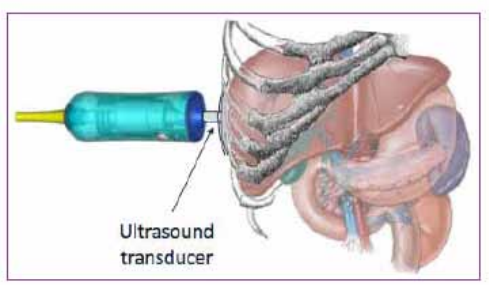
HCV Rx: And What About the Cost?

"…sofosbuvir alone is ±$80K for a 12 week course….the cost of therapy with high SVR rates may greatly offset the price required to manage the long-term complications and indirect effects of chronic HCV infection."

Moore C, Flamm S "The Price and Cost of Hepatitis C Treatment" Fam Pract News 2014; Feb 1:8-8



Fibroscan Non-Invasive Staging



Afdhal NH "Fibroscan (Transient Elastography) for the Measurement of Liver Fibrosis" Gastroenterology & Hepatology 2012;8(9):605-607

Transient Elastography (Fibroscan)

"…a non-invasive specialized ultrasound assessment that quantifies liver fibrosis and corresponds it to the equivalent in the METAVIR scoring system traditionally used in liver biopsies."

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Transient Elastography (Fibroscan)

"…and is increasingly used in place of liver Bx ….Many insurance companies use this score as a basis to determine eligibility for treatment."

Fort GG "Hepatitis C" *Ferri's Clinical Advisor* 2019;648-651

Fibrotest

- New to US: approved in France 2006
- US Tradename "FibroSure"
- Biomarker test: uses 6 biomarkers
- Similar prognostic value as liver Bx
  - HBV, HCV
  - Alcoholic liver disease
  - NAFLD
- Used for initial Dx, staging, and Rx f/u

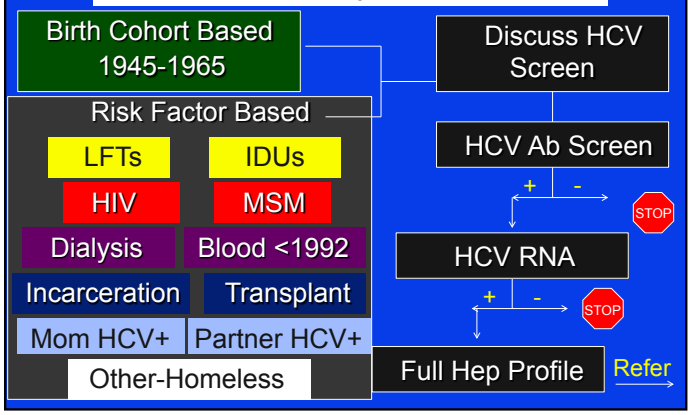
Wikipedia, accessed July 2014

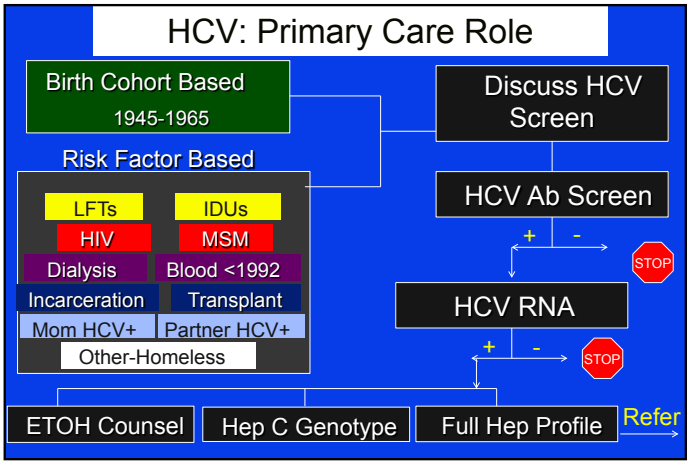
So What Do these Tests Cost?

Cost	Base	Low	High
Fibrosure	$215	$161	$269
Liver Bx	$1,255	$941	$1,569
FibroScan	$131	$98	$164

Carlson J et al J Gastroenterol Hepatol 2009;24(5):786-791

HCV: Primary Care Role





SELF EVALUATION

Screening for and Treating Hepatitis C

1. Which of the following is NOT a risk factor for Hepatitis C?

a. Marijuana use
b. Cocaine use
c. Transfusion <1992
d. Parenteral illicit drug use

2. According to the most recent CDC guidance, which population should be the primary target for Hepatitis C screening?

a. Immigrants from South America
b. Diabetics
c. Persons born between 1945-1965
d. Veterans

3. Prior to 1989, the virus we now know as Hepatitis C was called

a. Hepatitis Incognito
b. Non-A Non-B Hepatitis
c. Non-specific Hepatitis
d. Idiopathic Hepatitis

4. Why did the CDC switch the focus of hepatitis C screening from specific risk factors to birth cohort based screening?

a. Recognized risk factors are actually not very common in persons with chronic Hepatitis C
b. Persons with Hepatitis C are less than fully forthright about their risk factors
c. To de-stigmatize screening
d. b & c

5. The most common presentation of acute hepatitis C is

a. Fever with no other specific Sx
b. Nausea and vomiting
c. Jaundice
d. Subclinical (no remarkable Sx)

6. A patient born in 1956 is hepatitis C antibody positive, but hepatitis C RNA virus negative. This means

a. The hepatitis C antibody test is false+
b. The hepatitis C RNA test is false negative
c. The patient has chronic Hepatitis C
d. The patient has cleared Hepatitis C and is no longer infected

7. One of the partners of a newly married couple has chronic Hepatitis C. What is the annual risk of transmission with unprotected intercourse?

a. <1%
b. ±10%
c. ±30%
d. ±60%

Answer Key: 1. A, 2. C, 3. B, 4. D, 5. D, 6. D, 7. A

Richard A. Honaker, MD, FAAFP

Richard A. Honaker, MD, FAAFP, of Charlottesville, Virginia, is a board-certified, family practice physician who received his medical degree from the University of Virginia School of Medicine. Dr. Honaker has been listed in "Best Doctors", *D Magazine's* "Best Doctors in Dallas", *Texas Monthly's* "Texas Super Doctors", and Consumers' Research Council of America's "Guide to America's Top Family Doctors". He is a diplomate of the American Board of Family Medicine, has been in practice for over 30 years, and was the senior physician and president of a 10-provider group in a suburb of Dallas, Texas. Dr. Honaker was also co-founder of the Jefferson Physician Group, a prominent primary care IPA in Dallas, and has been a contributing medical columnist and commentator for numerous publications and many television and local news programs

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RICHARD A. HONAKER M.D., F.A.A.F.P.

Diplomate, American Board of Family Medicine

Boosting Practice Revenue, Efficiency and Patient Care – Parts 1 & 2

You Have Been Detected!!!

Your doctor has reviewed your medical chart
and found you are overdue for the following:

_____

_____

_____

Please call to schedule your appointment soon.

Dr. Detective Checklist

RH, JS, JH, MH, JRH, CAT, DF, GS, CT, DTF, JJ

PATIENT:_____ **DOB:**_____ **DATE:**_____

Do not pull charts on patients who are deceased, have been fired, are over 65 yo, or live out of state.

1. Needs the following:

- CP (age 20-100) . . . . . _____
- WCC (age 0-5) . . . . . _____
- YCP (age 6-12) . . . . . _____
- TCP (age 13-19) . . . . . _____
- WWE . . . . . _____
- IP . . . . . _____

2. Needs Office Visit for:

- **Blood Pressure**
  - BMP q 6 mos (on Diuretic) . . . . . _____
  - BMP, CBC q 6 mos (on ACEI) . . . . . _____
- **Depression**
  - HFPq 6mos . . . . . _____
- **Elevated Cholesterol**
  - HFP, LP q 6 mos . . . . . _____
- **Diabetes**
  - Hemoglobin AIC q 3 mos . . . . . _____
  - BMP & HFP (?) . . . . . _____
- **Thyroid**
  - TSH q 12 mos . . . . . _____

3. Needs a "no appointment" shot:

- Tetanus shot . . . . . _____
- Pneumonia shot . . . . . _____
- Hepatitis A shot . . . . . _____
- Hepatitis B shot (adolescents) . . . . . _____
- Meningitis shot . . . . . _____
- Other . . . . . _____

4. Needs the following Lab Test(s):

- CBC . . . . . _____
- HFP . . . . . _____
- Urinalysis . . . . . _____
- BMP . . . . . _____
- TSH . . . . . _____
- PSA . . . . . _____
- Other . . . . . _____

5. Needs the following:

- Pap Smear & Breast Exam . . . . . _____
- Chest X-ray . . . . . _____
- Exercise Stress Test . . . . . _____
- Colonoscopy . . . . . _____
- EKG . . . . . _____
- Bone Density Testing . . . . . _____
- Mammogram . . . . . _____
- Skin Exam . . . . . _____

6. Recall for _____ in _____ months. Recall entered: _____

7. Nothing needed. _____

PROVIDER _____ FILE ROOM _____ Notice and Forms sent to patient (date): _____

We Would Love To See You Back!

In reviewing your medical records, it has been brought to our attention that we have not seen you in our office as a patient in the last few years. We realize this may be due to your excellent health, a change in your insurance plan, or a move from the area.

If you made a change due to a new insurance plan, please check with us to see if we are on your current insurance. Enclosed is a list of insurance plans we are currently accepting. We can also see you out of network (see attached).

Our goal is to help you with your medical needs. We hope you agree that the best way to stay healthy is through prevention, early detection of disease, prompt treatment when necessary, and follow-up of medical problems.

Whether you choose our doctors or another medical practice, your health is important to us. Enclosed you will find our Preventive Medicine-Wellness Guidelines. This will let you know the recommended tests and procedures that should be performed on a regular basis for healthy adults and children.

We look forward to seeing you soon,

Name: _____
Date _____

- **REVIEW OF SYMPTOMS**

CHECK ☑ THE BOX FOR CURRENT PROBLEMS

Your 3 Main Problems: (1) _____(2) _____ (3) _____

General
- ☐ Fatigue/Weakness
- ☐ I do not feel rested when I wake up
- ☐ I am not satisfied with my sleep
- ☐ I am very sleepy during the day
- ☐ I fall asleep easily during the day
- ☐ Unhappiness
- ☐ Depression
- ☐ Have you been sad for much of the past year?
- ☐ Have you lost your joy in usual activities?
- ☐ Do you often feel sad or depressed?
- ☐ Tearfulness
- ☐ Feelings of worthlessness
- ☐ Concentration difficulty
- ☐ Excessive irritability
- ☐ Lack of motivation
- ☐ Moodiness
- ☐ Nervousness/Anxiety
- ☐ Always feel ill
- ☐ Unexplained fever > 100
- ☐ Night sweats
- ☐ Weight loss recent
- ☐ Weight gain
- ☐ Allergies
- ☐ Anemia
- ☐ Phobias
- ☐ Mental Illnesses

Skin
- ☐ I have a mole(s) I want you to check
- ☐ Changes in moles/unusual moles
- ☐ Are you concerned about skin spots/growths?
- ☐ Bruise easily
- ☐ Rashes
- ☐ Hives
- ☐ Itching
- ☐ Psoriasis
- ☐ Dry skin
- ☐ Excessive hair growth
- ☐ Hair Loss

Ears/Nose/Throat
- ☐ Allergy symptoms
- ☐ Frequent colds
- ☐ Decreased hearing
- ☐ Ringing in the ears
- ☐ Ear infections - frequent
- ☐ Dizzy spells - dizziness
- ☐ Nose Bleeds - frequent
- ☐ Sinus trouble
- ☐ Sore throat - frequent
- ☐ Hoarseness frequent
- ☐ I would like allergy testing

Eyes
- ☐ Watery eyes
- ☐ Itchy eyes
- ☐ Pain
- ☐ Double or blurred vision
- ☐ Other visual disturbances

Lungs
- ☐ Pneumonia
- ☐ Asthma/Wheezing
- ☐ Cough - persistent
- ☐ Coughing blood
- ☐ Snoring
- ☐ Sleep Apnea or Gasping
- ☐ TB/Positive TB skin test

Heart/Circulation
- ☐ Shortness of breath
  - ☐ On exertion ☐ Lying flat
- ☐ Chest Pain or Chest Discomfort
- ☐ High blood pressure
- ☐ Heart Murmur
- ☐ Palpitations/Racing heart
- ☐ Irregular pulse
- ☐ Swollen ankles
- ☐ Fainting spells
- ☐ Leg pain with walking
- ☐ Varicose veins
- ☐ Cold/Numb feet
- ☐ Phlebitis - Blood clots

Gastrointestinal
- ☐ Change in bowel habits - recent
- ☐ Indigestion or heartburn
- ☐ Loss of appetite - recent
- ☐ Difficulty swallowing
- ☐ Persistent nausea/vomiting
- ☐ Peptic ulcers
- ☐ Swallowing pain
- ☐ Abdominal pain
- ☐ Diarrhea
- ☐ Constipation
- ☐ Bloody or tarry stools
- ☐ Hemorrhoids
- ☐ Gallbladder problems
- ☐ Hepatitis/Jaundice
- ☐ Require laxative - How often?

Genital/Urinary
- ☐ Hernia
- ☐ Urine infections - frequent
- ☐ Painful urination
- ☐ Frequent urination
- ☐ Urinary leakage/Incontinence
- ☐ Blood in urine
- ☐ Overnight urination x 2
- ☐ Loss of control of urination
- ☐ History of sexually transmitted diseases?
- ☐ Are there sexual issues or dysfunctions you want to discuss?
- ☐ Loss of interest in sex

Male
- ☐ Decrease in force of urination
- ☐ Erection problems
- ☐ Too rapid ejaculation
- ☐ Testicle lumps/swelling

Female
- ☐ Pain/Bleeding during or after sex
- ☐ Vaginal discharge/itching
- ☐ Abnormal Pap smear
- ☐ Flushing/Menopause symptoms
- ☐ Significant pain/cramps with periods

Breast
- ☐ Pain
- ☐ Cysts
- ☐ Lumps/Nodules
- ☐ Nipple discharge
- ☐ Biopsy of a nodule/lump

Female Menstrual History
- ☐ Age of ____ Onset ☐ Reg ☐ Irreg
- ☐ Flow: ☐ Heavy ☐ Moderate ☐ Light
- ☐ _____ Days of flow ____ Length of cycle
- ☐ # of pregnancies _____
- ☐ # of live births _____
- ☐ # of miscarriages/other _____
- ☐ Birth control method _____

Central/Peripheral Nervous System
- ☐ Headaches - frequent
- ☐ Seizures/convulsions
- ☐ Stroke
- ☐ Memory loss
- ☐ Tremor/Hands shaking
- ☐ Dizzy/Lightheaded
- ☐ Muscle wasting
- ☐ Numbness/Tingling sensations

Musculoskeletal
- ☐ Arthritis
- ☐ Back pain - recurrent
- ☐ Bone pain/fracture
- ☐ Gout
- ☐ Foot pain

Miscellaneous
- ☐ Date of last tetanus booster shot _____
- ☐ Have you ever been physically hurt by your partner? ☐ Yes ☐ No
- ☐ Blood transfusion before 1992? ☐ Yes ☐ No
- ☐ Any tattoos? ☐ Yes ☐ No
- ☐ I want sexually transmitted discase testing? ☐ Yes ☐ No
- ☐ I want HIV testing? ☐ Yes ☐ No
- ☐ Frequent foreign travel? ☐ Yes ☐ No

I would like more information on
- ☐ Anti-aging skin Care products
- ☐ Skin care products to improve my skin
- ☐ Skin peels/microdermabrasion to improve my skin
- ☐ Acne skin care products
- ☐ Allergy testing

Other

Other diseases or symptoms or concerns

_____
_____
_____
_____

Explanation: _____

_____

Note to MD or PA: Write "P" next to any symptom discussed on Progress Note (P = PN)

PRACTICE EFFICIENCY, REVENUE ENHANCEMENT, PRACTICE JOY

NINE PROGRAMS:

Dr. Detective
Dr. Warm and Fuzzy
Dr. Miscellaneous
Dr. Marketing
Dr. Volume
Dr. Coding
Dr. Complete Physical
Dr. Skin
Dr. Recall

MODIFIERS:

-25
-51
-59

SPECIAL CODES

99058
99080
99051

OTHER

Shave biopsy - 11300 series

Excision-Benign lesions - 11400 Series

Excision - Malignant lesions - 11600 Series

Destruction -
17000
17003
17106
17110

Repair
12000-simple
12031-2-intermiate

Prolonged Care
99354-5
99358-9

Chemical cautery (e.g. silver nitrate)
17250
30901
40820

EKG
93000
93010
93015
93040

Injections
20550
20551
20552-3

Splinting and strapping
29280
29550

Paring
11055-6

Skin Tag Removal
11200

Burn Care
16000
16015
16020

Miscellaneous
11000
11100
11740
11900
20605
29130
54050
92599
94010
94060
99441-3
99444

99058: Office emergency care CPT® 99058: SERVICE(S) PROVIDED ON AN EMERGENCY BASIS IN THE OFFICE, WHICH DISRUPTS OTHER SCHEDULED OFFICE SERVICES, IN ADDITION TO BASIC SERVICE

99080: Special reports or forms CPT® 99080: SPECIAL REPORTS SUCH AS INSURANCE FORMS, MORE THAN THE INFORMATION CONVEYED IN THE USUAL MEDICAL COMMUNICATIONS OR STANDARD REPORTING FORM

99051: Med serv eve/wkend/holiday CPT® 99051: SERVICE(S) PROVIDED IN THE OFFICE DURING REGULARLY SCHEDULED EVENING, WEEKEND, OR HOLIDAY OFFICE HOURS, IN ADDITION TO BASIC SERVICE

99354: Prolong e&m/psyctx serv o/p CPT® 99354: PROLONGED EVALUATION AND MANAGEMENT OR PSYCHOTHERAPY SERVICE(S) (BEYOND THE TYPICAL SERVICE TIME OF THE PRIMARY PROCEDURE) IN THE OFFICE OR OTHER OUTPATIENT SETTING REQUIRING DIRECT PATIENT CONTACT BEYOND THE USUAL SERVICE; FIRST HOUR (LIST SEPARATELY IN ADDITION TO CODE FOR OFFICE OR OTHER OUTPATIENT EVALUATION AND MANAGEMENT OR PSYCHOTHERAPY SERVICE)

99358: Prolong service w/o contact CPT® 99358: PROLONGED EVALUATION AND MANAGEMENT SERVICE BEFORE AND/OR AFTER DIRECT PATIENT CARE; FIRST HOUR

99359: Prolong serv w/o contact add CPT® 99359: PROLONGED EVALUATION AND MANAGEMENT SERVICE BEFORE AND/OR AFTER DIRECT PATIENT CARE; EACH ADDITIONAL 30 MINUTES (LIST SEPARATELY IN ADDITION TO CODE FOR PROLONGED SERVICE)

30901: Control of nosebleed CPT®30901: CONTROL NASAL HEMORRHAGE, ANTERIOR, SIMPLE (LIMITED CAUTERY AND/OR PACKING) ANY METHOD

40820: Treatment of mouth lesion CPT® 40820: DESTRUCTION OF LESION OR SCAR OF VESTIBULE OF MOUTH BY PHYSICAL METHODS (EG, LASER, THERMAL, CRYO, CHEMICAL)

17250: Chemical cautery tissue CPT® 17250: CHEMICAL CAUTERIZATION OF GRANULATION TISSUE (PROUD FLESH, SINUS OR FISTULA)93040: Rhythm ecg with report CPT® 93040: RHYTHM ECG, 1-3 LEADS; WITH INTERPRETATION AND REPORT

93010: Electrocardiogram report CPT® 93010: ELECTROCARDIOGRAM, ROUTINE ECG WITH AT LEAST 12 LEADS; INTERPRETATION AND REPORT ONLY

93015: Cardiovascular stress test CPT® 93015: CARDIOVASCULAR STRESS TEST USING MAXIMAL OR SUBMAXIMAL TREADMILL OR BICYCLE EXERCISE, CONTINUOUS ELECTROCARDIOGRAPHIC MONITORING, AND/OR PHARMACOLOGICAL STRESS; WITH SUPERVISION, INTERPRETATION AND REPORT

93000: Electrocardiogram complete CPT® 93000: ELECTROCARDIOGRAM, ROUTINE ECG WITH AT LEAST 12 LEADS; WITH INTERPRETATION AND REPORT

94060: Evaluation of wheezing CPT® 94060: BRONCHODILATION RESPONSIVENESS, SPIROMETRY AS IN 94010, PRE- AND POST-BRONCHODILATOR ADMINISTRATION

94010: Breathing capacity test CPT® 94010: SPIROMETRY, INCLUDING GRAPHIC RECORD, TOTAL AND TIMED VITAL CAPACITY, EXPIRATORY FLOW RATE MEASUREMENT(S), WITH OR WITHOUT MAXIMAL VOLUNTARY VENTILATION

29130: Application of finger splint CPT® 29130: APPLICATION OF FINGER SPLINT; STATIC

99444: Online e/m by phys/qhp CPT® 99444: ONLINE EVALUATION AND MANAGEMENT SERVICE PROVIDED BY A PHYSICIAN OR OTHER QUALIFIED HEALTH CARE PROFESSIONAL WHO MAY REPORT EVALUATION AND MANAGEMENT SERVICES PROVIDED TO AN ESTABLISHED PATIENT OR GUARDIAN, NOT ORIGINATING FROM A RELATED E/M SERVICE PROVIDED WITHIN THE PREVIOUS 7 DAYS, USING THE INTERNET OR SIMILAR ELECTRONIC COMMUNICATIONS NETWORK99441: Phone e/m phys/qhp 5-10 min CPT® 99441: TELEPHONE EVALUATION AND MANAGEMENT SERVICE BY A PHYSICIAN OR OTHER QUALIFIED HEALTH CARE PROFESSIONAL WHO MAY REPORT EVALUATION AND MANAGEMENT SERVICES PROVIDED TO AN ESTABLISHED PATIENT, PARENT, OR GUARDIAN NOT ORIGINATING FROM A RELATED E/M SERVICE PROVIDED WITHIN THE PREVIOUS 7 DAYS NOR LEADING TO AN E/M SERVICE OR PROCEDURE WITHIN THE NEXT 24 HOURS OR SOONEST AVAILABLE APPOINTMENT; 5-10 MINUTES OF MEDICAL DISCUSSION

99442: Phone e/m phys/qhp 11-20 min CPT® 99442: TELEPHONE EVALUATION AND MANAGEMENT SERVICE BY A PHYSICIAN OR OTHER QUALIFIED HEALTH CARE PROFESSIONAL WHO MAY REPORT EVALUATION AND MANAGEMENT SERVICES PROVIDED TO AN ESTABLISHED PATIENT, PARENT, OR GUARDIAN NOT ORIGINATING FROM A RELATED E/M SERVICE PROVIDED WITHIN THE PREVIOUS 7 DAYS NOR LEADING TO AN E/M SERVICE OR PROCEDURE WITHIN THE NEXT 24 HOURS OR SOONEST AVAILABLE APPOINTMENT; 11-20 MINUTES OF MEDICAL DISCUSSION

99443: Phone e/m phys/qhp 21-30 min CPT® 99443: TELEPHONE EVALUATION AND MANAGEMENT SERVICE BY A PHYSICIAN OR OTHER QUALIFIED HEALTH CARE PROFESSIONAL WHO MAY REPORT EVALUATION AND MANAGEMENT SERVICES PROVIDED TO AN ESTABLISHED PATIENT, PARENT, OR GUARDIAN NOT ORIGINATING FROM A RELATED E/M SERVICE PROVIDED WITHIN THE PREVIOUS 7 DAYS NOR LEADING TO AN E/M SERVICE OR PROCEDURE WITHIN THE NEXT 24 HOURS OR SOONEST AVAILABLE APPOINTMENT; 21-30 MINUTES OF MEDICAL DISCUSSION

NO RESULTS FOR 92599

11300: Shave skin lesion 0.5 cm/< CPT® 11300: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, TRUNK, ARMS OR LEGS; LESION DIAMETER 0.5 CM OR LESS

11302: Shave skin lesion 1.1-2.0 cm CPT® 11302: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, TRUNK, ARMS OR LEGS; LESION DIAMETER 1.1 TO 2.0 CM11303: Shave skin lesion >2.0 cm CPT® 11303: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, TRUNK, ARMS OR LEGS; LESION DIAMETER OVER 2.0 CM

11305: Shave skin lesion 0.5 cm/< CPT® 11305: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, SCALP, NECK, HANDS, FEET, GENITALIA; LESION DIAMETER 0.5 CM OR LESS

11306: Shave skin lesion 0.6-1.0 cm CPT® 11306: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, SCALP, NECK, HANDS, FEET, GENITALIA; LESION DIAMETER 0.6 TO 1.0 CM

11307: Shave skin lesion 1.1-2.0 cm CPT® 11307: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, SCALP, NECK, HANDS, FEET, GENITALIA; LESION DIAMETER 1.1 TO 2.0 CM

11308: Shave skin lesion >2.0 cm CPT® 11308: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, SCALP, NECK, HANDS, FEET, GENITALIA; LESION DIAMETER OVER 2.0 CM

11310: Shave skin lesion 0.5 cm/< CPT® 11310: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, FACE, EARS, EYELIDS, NOSE, LIPS, MUCOUS MEMBRANE; LESION DIAMETER 0.5 CM OR LESS

11311: Shave skin lesion 0.6-1.0 cm CPT® 11311: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, FACE, EARS, EYELIDS, NOSE, LIPS, MUCOUS MEMBRANE; LESION DIAMETER 0.6 TO 1.0 CM

11312: Shave skin lesion 1.1-2.0 cm CPT® 11312: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, FACE, EARS, EYELIDS, NOSE, LIPS, MUCOUS MEMBRANE; LESION DIAMETER 1.1 TO 2.0 CM

11313: Shave skin lesion >2.0 cm CPT® 11313: SHAVING OF EPIDERMAL OR DERMAL LESION, SINGLE LESION, FACE, EARS, EYELIDS, NOSE, LIPS, MUCOUS MEMBRANE; LESION DIAMETER OVER 2.0 CM11400: Exc tr-ext b9+marg 0.5 cm< CPT® 11400: EXCISION, BENIGN LESION INCLUDING MARGINS, EXCEPT SKIN TAG (UNLESS LISTED ELSEWHERE), TRUNK, ARMS OR LEGS; EXCISED DIAMETER 0.5 CM OR LESS

11401: Exc tr-ext b9+marg 0.6-1 cm CPT® 11401: EXCISION, BENIGN LESION INCLUDING MARGINS, EXCEPT SKIN TAG (UNLESS LISTED ELSEWHERE), TRUNK, ARMS OR LEGS; EXCISED DIAMETER 0.6 TO 1.0 CM

11402: Exc tr-ext b9+marg 1.1-2 cm CPT® 11402: EXCISION, BENIGN LESION INCLUDING MARGINS, EXCEPT SKIN TAG (UNLESS LISTED ELSEWHERE), TRUNK, ARMS OR LEGS; EXCISED DIAMETER 1.1 TO 2.0 CM

11403: Exc tr-ext b9+marg 2.1-3 cm CPT® 11403: EXCISION, BENIGN LESION INCLUDING MARGINS, EXCEPT SKIN TAG (UNLESS LISTED ELSEWHERE), TRUNK, ARMS OR LEGS; EXCISED DIAMETER 2.1 TO 3.0 CM

11404: Exc tr-ext b9+marg 3.1-4 cm CPT® 11404: EXCISION, BENIGN LESION INCLUDING MARGINS, EXCEPT SKIN TAG (UNLESS LISTED ELSEWHERE), TRUNK, ARMS OR LEGS; EXCISED DIAMETER 3.1 TO 4.0 CM

11406: Exc tr-ext b9+marg >4.0 cm CPT® 11406: EXCISION, BENIGN LESION INCLUDING MARGINS, EXCEPT SKIN TAG (UNLESS LISTED ELSEWHERE), TRUNK, ARMS OR LEGS; EXCISED DIAMETER OVER 4.0 CM

11600: Exc tr-ext mal+marg 0.5 cm/< CPT(t!) 11600: EXCISION, MALIGNANT LESION INCLUDING MARGINS, TRUNK, ARMS, OR LEGS; EXCISED DIAMETER 0.5 CM OR LESS

11601: Exc tr-ext mal+marg 0.6-1 cm CPT® 11601: EXCISION, MALIGNANT LESION INCLUDING MARGINS, TRUNK, ARMS, OR LEGS; EXCISED DIAMETER 0.6 TO 1.0 CM

11602: Exc tr-ext mal+marg 1.1-2 cm CPT® 11602: EXCISION, MALIGNANT LESION INCLUDING MARGINS, TRUNK, ARMS, OR LEGS; EXCISED DIAMETER 1.1 TO 2.0 CM11603: Exc tr-ext mal+marg 2.1-3 cm CPT® 11603: EXCISION, MALIGNANT LESION INCLUDING MARGINS, TRUNK, ARMS, OR LEGS; EXCISED DIAMETER 2.1 TO 3.0 CM

11604: Exc tr-ext mal+marg 3.1-4 cm CPT® 11604: EXCISION, MALIGNANT LESION INCLUDING MARGINS, TRUNK, ARMS, OR LEGS; EXCISED DIAMETER 3.1 TO 4.0 CM

11606: Exc tr-ext mal+marg >4 cm CPT® 11606: EXCISION, MALIGNANT LESION INCLUDING MARGINS, TRUNK, ARMS, OR LEGS; EXCISED DIAMETER OVER 4.0 CM

17000: Destruct premalg lesion CPT® 17000: DESTRUCTION (EG, LASER SURGERY, ELECTROSURGERY, CRYOSURGERY, CHEMOSURGERY, SURGICAL CURETTEMENT), PREMALIGNANT LESIONS (EG, ACTINIC KERATOSES); FIRST LESION

17003: Destruct premalg les 2-14 CPT® 17003: DESTRUCTION (EG, LASER SURGERY, ELECTROSURGERY, CRYOSURGERY, CHEMOSURGERY, SURGICAL CURETTEMENT), PREMALIGNANT LESIONS (EG, ACTINIC KERATOSES); SECOND THROUGH 14 LESIONS, EACH (LIST SEPARATELY IN ADDITION TO CODE FOR FIRST LESION)

11000: Debride infected skin CPT® 11000: DEBRIDEMENT OF EXTENSIVE ECZEMATOUS OR INFECTED SKIN; UP TO 10% OF BODY SURFACE

17110: Destruct b9 lesion 1-14 CPT® 17110: DESTRUCTION (EG, LASER SURGERY, ELECTROSURGERY, CRYOSURGERY, CHEMOSURGERY, SURGICAL CURETTEMENT), OF BENIGN LESIONS OTHER THAN SKIN TAGS OR CUTANEOUS VASCULAR PROLIFERATIVE LESIONS; UP TO 14 LESIONS

11100: Biopsy skin lesion CPT® 11100: BIOPSY OF SKIN, SUBCUTANEOUS TISSUE AND/OR MUCOUS MEMBRANE (INCLUDING SIMPLE CLOSURE), UNLESS OTHERWISE LISTED; SINGLE LESION12031: Intmd rpr s/a/t/ext 2.5 cm/< CPT® 12031: REPAIR, INTERMEDIATE, WOUNDS OF SCALP, AXILLAE, TRUNK AND/OR EXTREMITIES (EXCLUDING HANDS AND FEET); 2.5 CM OR LESS

12041: Intmd rpr n-hf/genit 2.5 cm/< CPT® 12041: REPAIR, INTERMEDIATE, WOUNDS OF NECK, HANDS, FEET AND/OR EXTERNAL GENITALIA; 2.5 CM OR LESS

12032: Intmd rpr s/a/t/ext 2.6-7.5 CPT® 12032: REPAIR, INTERMEDIATE, WOUNDS OF SCALP, AXILLAE, TRUNK AND/OR EXTREMITIES (EXCLUDING HANDS AND FEET); 2.6 CM TO 7.5 CM

99213: Office/outpatient visit est CPT® 99213: OFFICE OR OTHER OUTPATIENT VISIT FOR THE EVALUATION AND MANAGEMENT OF AN ESTABLISHED PATIENT, WHICH REQUIRES AT LEAST 2 OF THESE 3 KEY COMPONENTS: AN EXPANDED PROBLEM FOCUSED HISTORY; AN EXPANDED PROBLEM FOCUSED EXAMINATION; MEDICAL DECISION MAKING OF LOW COMPLEXITY. COUNSELING AND COORDINATION OF CARE WITH OTHER PHYSICIANS, OTHER QUALIFIED HEALTH CARE PROFESSIONALS, OR AGENCIES ARE PROVIDED CONSISTENT WITH THE NATURE OF THE PROBLEM(S) AND THE PATIENT'S AND/OR FAMILY'S NEEDS. USUALLY, THE PRESENTING PROBLEM(S) ARE OF LOW TO MODERATE SEVERITY. TYPICALLY, 15 MINUTES ARE SPENT FACE-TO-FACE WITH THE PATIENT AND/OR FAMILY.

99214: Office/outpatient visit est CPT® 99214: OFFICE OR OTHER OUTPATIENT VISIT FOR THE EVALUATION AND MANAGEMENT OF AN ESTABLISHED PATIENT, WHICH REQUIRES AT LEAST 2 OF THESE 3 KEY COMPONENTS: A DETAILED HISTORY; A DETAILED EXAMINATION; MEDICAL DECISION MAKING OF MODERATE COMPLEXITY. COUNSELING AND/OR COORDINATION OF CARE WITH OTHER PHYSICIANS, OTHER QUALIFIED HEALTH CARE PROFESSIONALS, OR AGENCIES ARE PROVIDED CONSISTENT WITH THE NATURE OF THE PROBLEM(S) AND THE PATIENT'S AND/OR FAMILY'S NEEDS. USUALLY, THE PRESENTING PROBLEM(S) ARE OF MODERATE TO HIGH SEVERITY. TYPICALLY, 25 MINUTES ARE SPENT FACE-TO-FACE WITH THE PATIENT AND/OR FAMILY.

WHAT IS A COMPLETE PHYSICAL?

A complete physical has 5 parts:

1. **History** - A thorough review of your medical history, family history, medications, and surgeries. This includes a questionnaire with 145 questions about your personal medical history.
2. **Physical** - A head to toe examination, including a 70 point check off list and cancer check-up.
3. **Laboratory** - Approximately 60 different lab tests are run on 2 tubes of blood to screen for diseases.
4. **Health Promotion Guidelines** - A 10 page handout with a discussion of 46 specific health issues to help you live a longer and healthier life.
5. **Summary** - We will list your medical problems and give you specific suggestions and action steps.

How often should you have a physical?

- Every 2-3 years in your 20's and 30's.
- Every 1-2 years in your 40's.
- Every year beginning at 50.

YOUNG COMPLETE PHYSICAL (Ages 6-12)

Dear Parent:

Your 6 to 12-year-old children need a complete physical every year. It is very important that this be done even if your child is healthy.

This is a one-visit physical and requires your presence. It will not require blood work unless there is some problem found.

We will do a brief history, reviewing medical problems in your child and the family. We will do a physical looking for problems with ears, throat, heart murmurs, abdominal and internal organs, orthopedic issues, hernias, etc.

We will also recommend "health promotion" advice such as taking vitamins, avoiding junk food, etc, to help your child live a longer and healthier life.

Sincerely,

TEEN COMPLETE PHYSICAL (Ages 13-19)

Dear Parent:

Your teenager needs a complete physical every year. It is very important that this be done even if they are healthy.

This is a two-part evaluation. The first visit requires your presence. We may do some lab work, so your teenager should have only a light breakfast or lunch.

The second visit is a physical exam and discussion of health issues. You may be present for part of this visit if you wish. However, we want some time alone with your teen to discuss issues regarding drugs, alcohol, and perhaps sexuality issues.

This two-part physical involves a review of the family and patient's medical history and any symptoms that your teenager may have. The physical exam will be a complete examination looking for any problems. We will possibly do some lab tests to check for anemia, cholesterol, etc. We will also give them a 10-page handout, which discusses many specific health issues to help your teenager live a longer and healthier life.

Sincerely,

NOTE: While your presence is optional for your 18 or 19-year-old, it would be beneficial to have you there at the first visit to obtain an accurate medical history.

SELF EVALUATION

Boosting Practice Revenue, Efficiency and Patient Care – Parts 1 & 2

True/False

1. When you perform an E/M service on the same day as a Preventive Service, you should attach modifier-25 on the Preventive Code.

2. It is acceptable to submit an E/M fee on the same day as a procedure, as long as a significant, separately identifiable service is also performed and documented properly.

3. The code for condyloma destruction is 17000.

4. The code for destruction of a wart is 17110.

5. Almost all patients will call back to schedule an appointment when they say they will.

6. A verbal instruction to a patient works better than a handout or email.

7. An intermediate layered closure of a biopsy site wound is coded according to the diameter of the lesion removed.

8. For the emergent code, 99058, it is best to document that the provider was interrupted from his/her schedule to see the patient.

9. For skin procedure codes, often there are different codes for arms/legs vs hand/feet.

10. For procedures on small lesions, it is best to measure in millimeters rather than centimeters.

11. Patients do not make judgments of your clinical quality based on the appearance of your office.

12. It is a good idea to always charge patients who No Show for their appointment.

13. PCP's only want Specialists to notify them of their patient's hospital admission after discharge.

14. Bibliotherapy is an underutilized technique to improve patient care.

ANSWER KEY: 1. F, 2. T, 3. F, 4. T, 5. F, 6. F, 7. F, 8. T, 9. T, 10. T, 11. F, 12. F, 13. F, 14. T

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Evidence-Based Management of Patients with Type 2 Diabetes

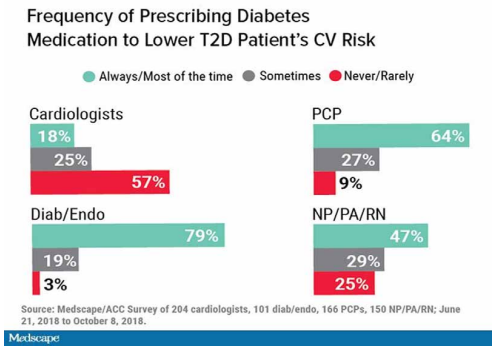
New ADA/EASD Guidance on Diabetes

- **The treatment approach to type 2 diabetes should begin with an assessment of cardiovascular disease (CVD) status, other comorbidities, and patient preferences, according to the 2018 joint consensus statement from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD).**
  - October 5, 2018 at the EASD annual meeting in Berlin and published in Diabetes Care and Diabetologia.

New ADA/EASD Guidance on Diabetes

- **Lifestyle modification and metformin are still considered the cornerstones of treatmen**t, although the panel did debate the ongoing role of metformin as the first-line pharmacologic therapy. Ultimately they opted to stick with the recommendation for now because of low cost and proven safety and efficacy.
- Then, **for patients in whom ASCVD predominates, a GLP-1 receptor agonist with proven CVD benefit or SGLT2 inhibitor with proven CVD benefit (provided the patient has adequate kidney function) are recommended, in that order.**
- **The order is reversed in patients for whom heart failure predominates: listed first is an SGLT2 inhibitor with evidence of reducing heart failure in a cardiovascular outcomes trial (if the patient has adequate kidney function), with a GLP-1 receptor agonist with proven CVD benefit as an alternative option.**
  - October 5, 2018 Diabetes Care. doi:10.2337/dci18-0033

Addressing CV Risk (Medscape/ACC Survey) February 25, 2019

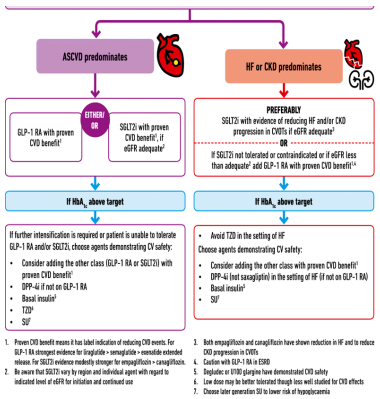


New ADA/EASD Guidance on Diabetes

- **Within the classes, preference is given to liraglutide among GLP-1 receptor agonists based on the LEADER trial, and empagliflozin among SGLT2 inhibitors based on EMPA-REG OUTCOME.**
- **For patients without ASCVD or heart failure, the next priority is to focus on the individual patient's needs and preferences for avoiding weight gain and hypoglycemia**. The document provides guidance for specific agents.
  - October 5, 2018 Diabetes Care. doi:10.2337/dci18-0033

New ADA/EASD Guidance on Diabetes

- **They were careful to discuss the limitations of the evidence. Including the caveat that "beyond dual therapy is an evidence-free zone," and the emphasis that the cardiovascular benefits of SGLT2 inhibitors and GLP-1 receptor agonists have only been proven in patients with established CVD.**
- They also included a "stop light" graphics indicating which medications should be stopped or reduced once other drugs are added, noting, "This is a common question we get from primary care providers about therapy intensification."



Prevention or Delay of Type 2 Diabetes 2019

- **Patients with prediabetes should be referred to an intensive behavioral lifestyle intervention program modeled on the Diabetes Prevention Program to achieve and maintain 7% loss of initial body weight and increase moderate intensity physical activity (such as brisk walking) to at least 150 min/week. A**
- Pharmacologic Intervention: **Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI ≥35 kg/m2, those aged < 60 years, and women with prior gestational diabetes mellitus. A**
  - **Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitaminB12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B**
  - Diabetes Care 2019 Jan; 42(Supplement 1): S29-S33.

2019 ADA Standards of Medical Care in Diabetes

Pharmacologic Therapy Recommendations

- **Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A**
- **Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. A**
  - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

- **A patient-centered approach should be used to guide the choice of pharmacologic agents**. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. E
- Among **patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium–glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit are recommended** as part of the antihyperglycemic regimen. A
  - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

- 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%) or blood glucose levels (≥300 mg/dL) are very high. E**
- **Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5% above their glycemic target. E**
  - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

- Among **patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium–glucose cotransporter 2 inhibitors are preferred. C**
- For **patients with type 2 diabetes and chronic kidney disease, consider use of a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. C**
  - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

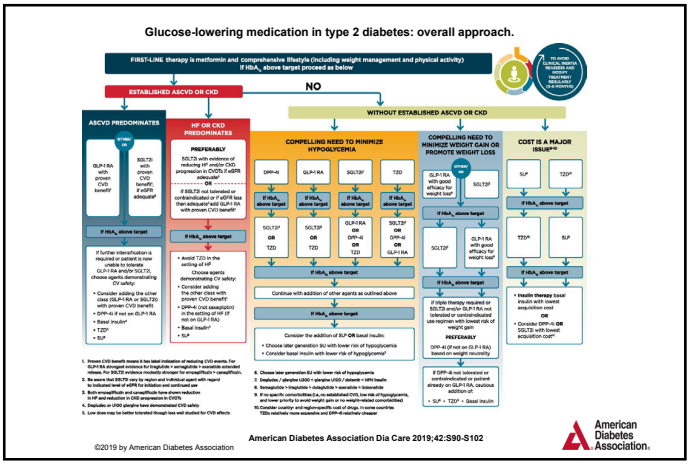
2019 ADA Standards of Medical Care in Diabetes

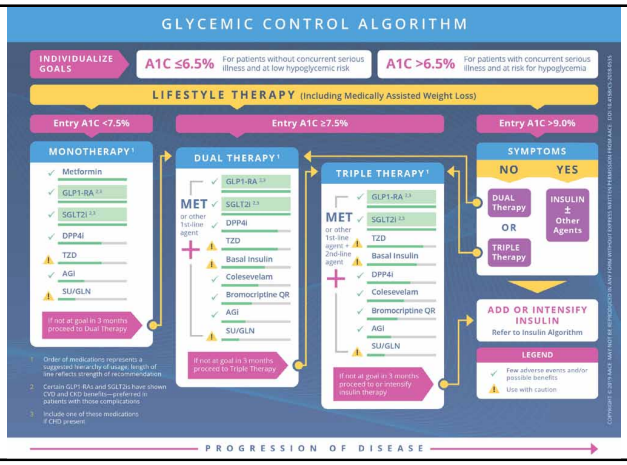
- **In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. B**
- Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B
  - Diabetes Care 2019 Jan; 42(Supplement 1): S90-S102

2019 ADA Standards of Medical Care in Diabetes

A1C Recommendations

- **A reasonable A1C goal for many nonpregnant adults is <7%. A**
- Providers might reasonably **suggest more stringent A1C goals (such as <6.5%) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment** (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease. C
- **Less stringent A1C goals (such as <8% may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes** in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin. B
  - Diabetes Care 2019 Jan; 42(Supplement 1): S61-S70





UK Prospective Diabetes Study
Glucose Interventional Trial

Outcome at 10 years	Diet/Met	Diet/Sulf/ Insulin	Diet	RRR/ARR/NNT (Diet/Met vs. Diet)
Any DM related endpoint	28.7%	36.8%	38.9%	26.2%/10.2%/10
Diabetes related death	8.2%	10.8%	13.4%	38.8%/5.2%/19
All cause mortality	14.6%	20%	21.7%	32.7%/7.1%/14
MI	11.4%	14.6%	17.8%	36%/6.4%/16
Stroke	3.5%	6.3%	5.6%	44.4%/2.8$/36
Micro-vascular events	7.0%	7.8%	9.2%	N/S

*UKPDS 80. N Eng J Med 2008; **359**:*

ukpds-ptm

Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus Treated with Insulin

Arch Intern Med. 2009;169(6):616-625

- **390 patients treated with insulin in the outpatient clinics of 3 hospitals in a randomized, placebo-controlled trial with a follow-up period of 4.3 years. Either metformin hydrochloride, 850 mg, or placebo (1-3 times daily) was added to insulin therapy.**
- The **primary end point was an aggregate of microvascular and macrovascular morbidity and mortality. The secondary end points were microvascular and macrovascular morbidity and mortality independently.**
  - "Hyperinsulinemia the Outcome of its Metabolic Effects (**HOME**))"

Long-term Effects of Metformin on Metabolism and Microvascular and Macrovascular Disease in Patients With Type 2 Diabetes Mellitus Treated with Insulin

Arch Intern Med. 2009;169(6):616-625

Results:

- **Metformin treatment prevented weight gain (mean weight gain, −3.07 kg [range, −3.85 to −2.28 kg]; *P*.001),**
- **Improved glycemic control (mean reduction in HbA1c level, 0.4% percentage point [95% CI, 0.55-0.25]; *P*.001),** despite the aim of similar glycemic control in both groups,
- **Reduced insulin requirements (mean reduction, 19.63 IU/d [95% CI, 24.91-14.36 IU/d]; *P*.001).**
- **Metformin was not associated with an improvement in the primary end point.**
- **It was, however, associated with an improvement in the secondary, macrovascular end point (hazard ratio, 0.61 (95% CI, 0.40-0.94; *P*=.02),** which was partly explained by the difference in weight.
- **The number needed to treat to prevent 1 macrovascular end point was 16.1 (95% CI, 9.2-66.6).**
- **These sustained beneficial effects support the policy to continue metformin treatment after the introduction of insulin in any patient with DM2, unless contraindicated.**

FDA Updates Metformin Dosing Information 4-8-2016

- **Before starting metformin, obtain the patient's eGFR.**
- **Metformin is contraindicated in patients with an eGFR below 30 mL/minute/1.73 m2.**
- **Starting metformin in patients with an eGFR between 30-45 mL/minute/1.73 m2 is not recommended**.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls below 45 mL/minute/1.73 m2, assess the benefits and risks of continuing treatment. **Discontinue metformin if the patient's eGFR later falls below 30 mL/minute/1.73 m2.**
- **Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/minute/1.73 m2**; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.
  - http://www.fda.gov/downloads/Drugs/DrugSafety/UCM494140.pdf

Metformin Pricing?

- Glucophage AB 500 mg/60: $68.00; 850 mg $115.00; 1000 mg $136.00
- **Generic Glucophage AB 500 mg/60 $0.00-12.00; 850 mg and 1000 mg $0.00-12.00**
- Glucophage XR AB1 500 mg/60 $70.00; 750 mg $100.00
- **Generic Glucophage XR AB1 500 mg/60 $4-12.00; 750 mg $10-20.00**
- **Glumetza AB3 500 mg/60 $3,250.00; 1000 mg/60 $6,800-7,200.00 (Santarus)**
- **Generic Glumetza AB3 500 mg/60 $750 - 1500.00; 1000 mg/60 $1,500.00-5,512.00 (Lupin, Sun and Activis)**
- **Fortamet AB2 500 and 1000 mg/60 $2,100.00 (Andrx)**
- **Generic Fortamet AB2 1000 mg/60 $400.00-$775.00 (Lupin and Mylan)**
  - GoodRx.com 1-4-2018

Empagliflozin (Jardiance) New Indication

December 2, 2016

- The U.S. Food and Drug Administration today approved **a new indication for empagliflozin (Jardiance) to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.**
- Based on a post market **Empa Reg Outcome trial of more than 7,000 patients with type 2 diabetes and cardiovascular disease**. In the trial, empagliflozin was **shown to reduce the risk of cardiovascular death compared to a placebo when added to standard of care therapies for diabetes and atherosclerotic cardiovascular disease.**

EMPA-REG OUTCOME Trial

- The **primary outcome (CV mortality, non-fatal MI and non-fatal stroke)** occurred in 490 of 4687 patients **(10.5%) in the pooled empagliflozin group** and in 282 of 2333 patients **(12.1%) in the placebo group** (hazard ratio in the empagliflozin group, **0.86**; 95.02% confidence interval, 0.74 to 0.99; **P=0.04 for superiority**).
  - **Median follow-up 3.1 years**
  - **ARR = 1.6%, NNT 63**
  - **No significant differences in rates of MI or CVA**
  - **No significant difference with 10 vs. 25 mg doses.**
  - **Death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction; ARR = 2.2%, NNT 46**
    - N Engl J Med 2015;373:2117-28

EMPA-REG OUTCOME Trial

- **Hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction) NNT 72**
- **Death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction) NNT 39**
- **Among patients receiving empagliflozin, there was an increased rate of genital infection (1 in 20 or 5%) but no increase in other adverse events. NNH 20**
  - N Engl J Med 2015;373:2117-28

EMPA-REG OUTCOME Trial: Renal Data

Microvascular Outcome

- **The prespecified composite microvascular outcome in the overall trial population occurred** in 577 of 4132 patients **(14.0%) in the empagliflozin group** and in 424 of 2068 patients **(20.5%) in the placebo group**, a **significant RRR 38% ARR 6.5%, NNT=16**
  - **the overall result for this composite microvascular outcome was driven entirely by the renal component**

NEJM on-line June 14, 2016

Canagliflozin: CANVAS and CANVAS R Trials

- Integrated data from two trials involving a total of **10,142 participants with type 2 diabetes and high cardiovascular risk (65.6% had a history of ASCVD).** Participants in each trial were randomly assigned to receive **canagliflozin or placebo and were followed for a mean of 188.2 weeks (3.62 years).**
- **The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (3 point MACE).**
  - **Initially tested for non-inferiority (p<0.001) and then if appropriate for superiority (p=0.02)**
  - N Engl J Med 2017; 377:644-657

Canagliflozin: CANVAS and CANVAS R Trials

- **Primary end-point (CV death, non-fatal MI and non-fatal stroke) 26.9 events/1000 pt years canagliflozin vs. 31.5 placebo; HR = 0.86 (95% CI 0.75-0.97); NNT = ~200**
- Secondary end-points **(events/1000 patient years)**
  - CV death 11.6 vs 12.8; HR = 0.87 (95% CI 0.72-1.06) NS
  - Non-fatal MI 9.7 vs. 11.6; HR = 0.85 (95% CI 0.69-1.05) NS
  - Non-fatal stroke 7.3 vs. 8.4; HR = 0.90 (95% CI 0.71-1.15) NS
  - **Hospitalization for heart failure 0.5 vs. 0.9; HR = 0.67 (95% CI 0.52-0.87); NNT = ~250**
  - Death any cause 17.3 vs. 19.5; HR = 0.87 (95% CI 0.74- 1.01) NS
    - N Engl J Med 2017; 377:644-657

Canagliflozin: CANVAS and CANVAS R Trials

- Diabetic ketoacidosis: 0.6/1000 pt. yrs. vs. 0.3 (p=0.14 NS)
- **Amputations: 6.3/1000 pt. yrs. vs. 3.4 (p<0.001) NNH = ~300**
- **Fractures (all): 15.4/1000 pt. yrs. vs. 11.9 (p=0.02) NNH = ~286**
- **Volume depletion: 26/1000 pt. yrs. vs. 18.5 (p=0.009) NNH = ~140**
- **Infection of male genitalia : 34.9/1000 pt. yrs. vs. 10.8 (p<0.001) NNH = ~42**
- **Female mycotic genital infection: 68.8/1000 pt. yrs. vs. 17.5 (p<0.001) NNH = ~19**
  - N Engl J Med 2017; 377:644-657

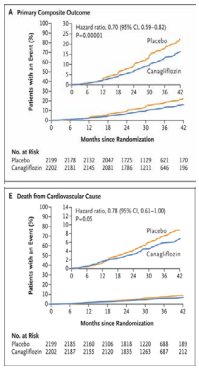
New FDA Safety Alert

- **[5-16-2017]: "Based on new data from two large clinical trials (CANVAS and CANVAS-R), the FDA has concluded that the type 2 diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR) causes an increased risk of leg and foot amputations. We are requiring new** warnings, including our most prominent **Boxed Warning**, to be added to the canagliflozin drug labels to describe this risk."
- Before initiating canagliflozin, **consider factors in the patient's history that may predispose them to the need for amputations**, such as a **history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers.**
  - **https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf**

Credence Trial

- A double-blind, randomized trial **in 4401 patients with type 2 diabetes and albuminuric chronic kidney disease** were randomized to receive **canagliflozin 100 mg daily or placebo**. All the patients had an estimated glomerular filtration rate **(eGFR) of 30 to <90 ml** per minute per 1.73 m2 of body-surface area and albuminuria (**ratio of albumin [mg] to creatinine [g], >300 to 5000)** were **treated with renin–angiotensin system blockade.** The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically. Trial stopped early.
  - NEJM 4-14-2019 (published on line)

Credence Trial



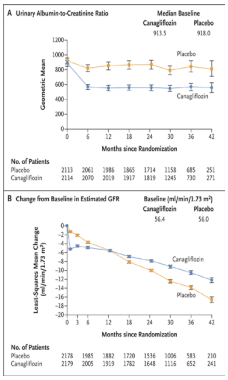
Primary outcome (primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes.
RRR 30% NNT 22 at 2.6 years

Table 2. Efficacy and Safety.*

Variable	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	P Value
	no./total no.		events/1000 patient-yr			
Efficacy						
Primary composite outcome	245/2202	340/2199	43.2	61.2	0.70 (0.59–0.82)	0.00001
Doubling of serum creatinine level	118/2202	188/2199	20.7	33.8	0.60 (0.48–0.76)	<0.001
End-stage kidney disease	116/2202	165/2199	20.4	29.4	0.68 (0.54–0.86)	0.002
Estimated GFR <15 ml/min/1.73 m²	79/2202	125/2199	13.6	22.2	0.60 (0.45–0.80)	NA
Dialysis initiated or kidney transplantation	76/2202	100/2199	13.3	17.7	0.74 (0.55–1.00)	NA
Renal death	2/2202	5/2199	0.3	0.9	NA	NA
Cardiovascular death	110/2202	140/2199	19.0	24.4	0.78 (0.61–1.00)	0.05

NEJM 4-14-2019 (published on-line)

Credence Trial



The geometric **mean of the urinary albumin-to-creatinine ratio was lower by 31% (95% CI, 26 to 35) on average during follow-up in the canagliflozin group**

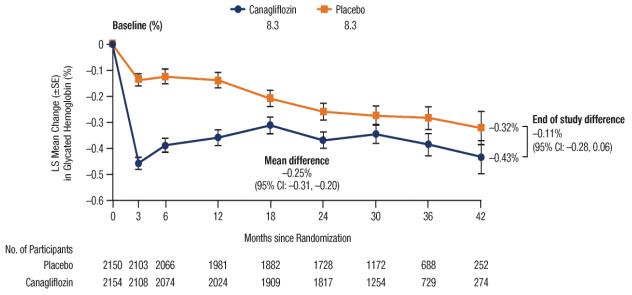
The least-squares mean (±SE) change in **the estimated GFR slope was less in the canagliflozin group than in the placebo group** (–3.19±0.15 vs. –4.71±0.15 ml per minute per 1.73 m2 per year), for a between-group difference of 1.52 ml per minute per 1.73 m2 per year (95% CI, 1.11 to 1.93). **During the first 3 weeks, there was a greater reduction in the estimated GFR in the canagliflozin group than in the placebo group** (–3.72±0.25 vs. –0.55±0.25 ml per minute per 1.73 m2),

NEJM 4-14-2019 (published on-line)

Credence Trial

- **Amputation - Canagliflozin 70/2200 vs. Placebo 63/2197 (3.2% vs. 2.87%) HR 1.11 (0.79–1.56) NS**
- **Fracture - Canalizflozin 67/2200 vs. Placebo 68/2197 (3.05% vs. 3.1%) HR 0.98 (0.70–1.37) NS**
- **Ketoacidosis - Canagliflozin 11/2200 vs. Placebo 1/2197 (0.5% vs. 0.05%) HR 10.80 (1.39–83.65) NNH 222**
  - NEJM 4-14-2019 (published on-line)

Credence Trial



For **glycated hemoglobin**, the least-squares mean level **at 13 weeks was lower in the canagliflozin group than in the placebo group by 0.31 percentage points** (95% CI, 0.26 to 0.37), and the between-group difference narrowed thereafter

NEJM 4-14-2019 (published on-line) Supplemental Appendix

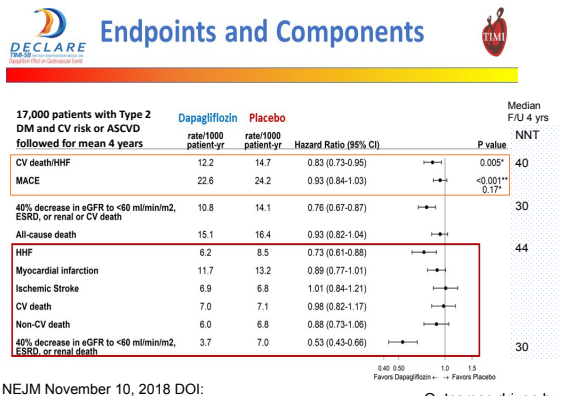
Credence Trial

- **4-14-2019 The National Kidney Foundation stated "If this supplemental indication is approved by the Food and Drug Administration (FDA), it would be the first new treatment for diabetic kidney disease (DKD) in decades."**
- We look forward to data in patients without diabetes but with CKD as well as those with eGFR less than 30 ml/min.
- Current **SGLT-2 class data suggest reduced efficacy in lowering A1c with decreasing eGFR.**
- Will , results of Credence change our guidelines?

DECLARE-TIMI-58 Trial

- Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes
- A Phase III cardiovascular (CV) outcomes trial (CVOT) for dapagliflozin (Farxiga), the broadest SGLT2 inhibitor CVOT conducted to date. The trial evaluated the **CV outcomes of dapagloflozin vs. placebo over a period of up to five years (median 4 years), across 33 countries and in more than 17,000 adults with type-2 diabetes (T2D) who have multiple CV risk factors (59.4% had at least one RF of dyslipidemia, HBP or smoking) or established CV disease (40.6% had ASCVD upon entry).**
- Mean A1c 8.3% +/- 1.2%, mean age 63.8 yrs +/- 6.8 yrs; duration of diabetes 11.8 +/- 7.8 yrs, 62.6% male and body mass index 32.1 ± 6.0 kg/m2
  - Diabetes Obes Metab. 2018 May;20(5):1102-1110

Endpoints and Components



NEJM November 10, 2018 DOI: 10.1056/NEJMoa1812389

*P for superiority, **P for non-inferiority

Outcomes driven by hospitalization for heart failure and renal effects

ADA 2019 Standards of Medical Care in Diabetes Update 3/28/2019

- Several revisions **based on the Dapagliflozin Effect on Cardiovascular Events - Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, in which the sodium-glucose cotransporter type 2 (SGLT2) inhibitor dapagliflozin (Farxiga, AstraZeneca) reduced hospitalization for heart failure and progression in chronic kidney disease (CKD).**
- Also regarding **dapagliflozin** use in section 11, a revision reflects the **recent label change to include approved use in CKD down to an eGRR ≥ 45 mL/min/1.73 m2 (previously ≥ 60 mL/min/1.73 m2).**
  - Under this new process, the online version of the Standards and downloadable PDF are updated and revised throughout the year with highlighted annotations added to the text.

FDA Safety Announcement

- [5-15-2015] **The FDA is warning that the SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin may lead to ketoacidosis**, a serious condition where the body produces high levels of blood acids called ketones that may require hospitalization.
- Patients should pay close attention for any **signs of ketoacidosis** and seek medical attention immediately if they experience **symptoms such as difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness**.

SGLT-2 Inhibitors and DKA

- A new analysis from Wake Forest, UNC and Duke) found **39 cases of DKA among 11,197 people with prescriptions for SGLT2 inhibitors (74% in patients with Type 2 DM/ 82% C; 15% D and 3% E). Of these, 26 patients had glucose ≤300 mg/dL, with a mean glucose of 266 mg/dL.** Symptoms reported included **nausea and vomiting (49%),** although researchers said "it is unclear if that was a cause, contributor, or consequence of the DKA." Also**, 67% of the patients had some other obvious event such as surgery, an insulin dose reduction, or weight loss.**
- The authors recommend "**a high index of suspicion for DKA in patients taking SGLT2 inhibitors with unexplained malaise or gastrointestinal symptoms and recommend measuring urine or plasma ketones in that setting,"**
  - Diabetes Care 2017 Mar 28 dc162591.

Concerns with SGLT-2 Inhibitors?

- I would not routinely recommend an SGLT-2 inhibitor in the following patients:
  - **Patients with impaired renal function (eGFR of < 45 ml/min maybe less than 30?).**
  - **Patients with diabetic neuropathy, previous foot ulcers, previous amputations and/or peripheral vascular disease.**
  - **Patients at risk for falls or with orthostatic hypotension.**
  - **Patients with a history of osteoporosis, osteopenia, decreased BMD or history of fractures.**

SGLT-2 Inhibitors and Necrotizing Fasciitis of the Perineum MedWatch 8-29-2018

- FDA is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This **serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene.** We are **requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors** and to the patient Medication Guide.
- **In the five years from March 2013 to May 2018, the FDA identified 12 cases (7 men and 5 women) of Fournier's gangrene in patients taking an SGLT2 inhibitor.** This number includes only reports submitted to FDA and found in the medical literature.

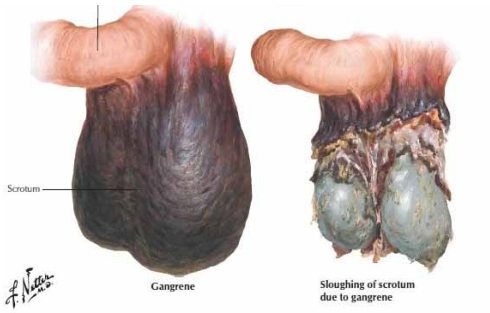
SGLT-2 Inhibitors and Fournier's Gangrene

- **UPDATE:** The **FDA identified 55 unique cases of FG in patients receiving SGLT2 inhibitors between 1 March 2013 and 31 January 2019.** The patients ranged in age from 33 to 87 years; 39 were men, and 16 were women. **Time to onset after initiation of SGLT2-inhibitor therapy ranged from 5 days to 49 months. All patients had surgical debridement and were severely ill.** Reported complications included diabetic ketoacidosis (n = 8), sepsis or septic shock (n = 9), and acute kidney injury (n = 4). Eight patients had fecal diversion surgery, 2 patients developed necrotizing fasciitis of a lower extremity that required amputation, and 1 patient required a lower-extremity bypass procedure because of gangrenous toes. **Three patients died.**
  - Ann Intern Med. [Epub ahead of print 7 May 2019] doi: 10.7326/M19-0085

SGLT-2 Inhibitors and Necrotizing Fasciitis of the Perineum MedWatch 8-29-2018

- The FDA identified 19 FG cases associated with other antiglycemic agents between 1984 and 31 January 2019.
- **Patient Information: Seek medical attention immediately if you experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell. These symptoms can worsen quickly.**

Fournier's Gangrene

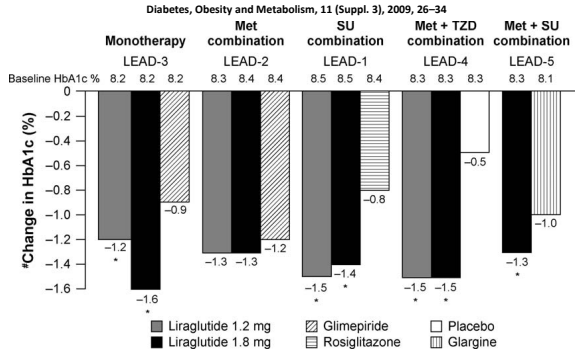


Liraglutide (Victoza) by Novo-Nordisk

- A human analog of the glucagon-like peptide-1 (GLP-1) with 97% amino acid sequence homology to endogenous human GLP-1.
  - T1/2 ~11-15 hrs
  - **1.2 mg dose (2 pens/mo)**
    - **$497.00 GoodRx.com**
  - **1.8 mg dose (3 pens/mo)**
    - **$743.00 GoodRx.com**
  - Adjunct to diet and exercise for Type 2 DM but not first line and no data in combo with prandial insulin

Liraglutide with or without oral antidiabetic drug therapy in type 2 diabetes: an overview of the LEAD 1–5 studies

Diabetes, Obesity and Metabolism, 11 (Suppl. 3), 2009, 26–34



LEADER CV Safety Trial with Liraglutide

- **9340 patients with type 2 diabetes and high cardiovascular risk** to receive liraglutide or placebo. **The primary composite** outcome in the time-to-event analysis **was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.**
  - **The median follow-up was 3.8 years.**
- **The primary outcome** occurred in significantly fewer patients in the **liraglutide** group (608 of 4668 patients **[13.0%]**) than in the **placebo** group (694 of 4672 **[14.9%]**) **(HR 0.87;** 95% CI , 0.78 to 0.97; **P<0.001 for noninferiority; P = 0.01 for superiority) ARR 1.9%, NNT=53**
  - N Engl J Med 2016; 375:311-322July 28, 2016

LEADER CV Safety Trial with Liraglutide

- **Death from cardio-vascular causes** in the **liraglutide** group (219 patients **[4.7%]**) than in the **placebo** group (278 **[6.0%]**) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P = 0.007). **ARR 1.3%, NNT 77**
- The rate of **death from any cause** was lower in the **liraglutide** group (381 patients **[8.2%]**) than in the **placebo** group (447 **[9.6%]**) (HR 0.85; 95% CI, 0.74 to 0.97; P = 0.02). **ARR 1.4%, NNT=72**
  - N Engl J Med 2016; 375:311-322July 28, 2016

LEADER CV Safety Trial with Liraglutide

- The rates of **nonfatal myocardial infarction (HR 0.88), nonfatal stroke (HR 0.89), and hospitalization for heart failure (HR 0.87) were all nonsignificantly lower in the liraglutide group than in the placebo group.**
  - N Engl J Med 2016; 375:311-322July 28, 2016
- **FDA approved 10/2017 to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease.**

LEADER CV Safety Trial with Liraglutide

- Microvascular Outcomes: The incidence of a **composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84; 95% CI, 0.73 to 0.97; P= 0.02)**
  - The difference that was **driven by a lower rate of nephropathy events in the liraglutide group (1.5 vs. 1.9 events per 100 patient-years of observation; HR 0.78**; 95% CI, 0.67 to 0.92; P = 0.003)
  - The incidence of **retinopathy events was nonsignificantly higher in the liraglutide group than in the placebo group (0.6 vs. 0.5 events per 100 patient-years; HR 1.15**; 95% CI, 0.87 to 1.52; P = 0.33).
    - N Engl J Med 2016; 375:311-322July 28, 2016

LEADER CV Safety Trial with Liraglutide

- The **most common adverse events leading to the discontinuation of liraglutide** were **gastrointestinal events**. The incidence of **pancreatitis was non-significantly lower in the liraglutide group (18 vs. 23)** than in the placebo group.
  - **Pancreatic carcinoma 13 (0.3) with liraglutide vs. 5 (0.1) with placebo p=0.06 ?Potential concern?**
  - **Medullary thyroid carcinoma 0 with liraglutide vs. 1 (<0.1) with placebo p=0.32**
    - N Engl J Med 2016; 375:311-322July 28, 2016

Dulaglutide – Trulicity by Lilly

- **Available in 0.75-mg and 1.5-mg single-dose pens which do not require mixing, measuring or needle attachment and can be administered any time of day.**
  - Insert states that for added comfort patients may want to take the pen out of the refrigerator for ~30 min prior to administration (DO NOT microwave or run under hot water)
- **Box of 4 pens (either dose) ~$750.00 retail (GoodRx.com)**

Dulaglutide – Trulicity

- **AWARD 6**- At the primary endpoint of 26 weeks, **once-weekly dulaglutide 1.5 mg and once-daily liraglutide 1.8 mg significantly reduced HbA1c levels from baseline (-1.42 percent and -1.36 percent, respectively),** with dulaglutide demonstrating non-inferiority compared to liraglutide. **A similar majority of patients in both treatment groups (68 percent) reached the American Diabetes Association's recommended HbA1c target of less than 7 percent**. Patients treated with once-weekly dulaglutide and once-daily liraglutide showed significant **weight reductions from baseline (-2.9 kg, -3.6 kg, respectively).** This weight reduction was **statistically greater in the liraglutide treatment arm.**
  - The Lancet, Early Online Publication, 11 July 2014 doi:10.1016/S0140-6736(14)60976-4

Dulaglutide (Trulicity)

- FDA required **Rewind (Researching cardiovascular Events with a Weekly INcretin in Diabetes) CV safety trial ~9600 patients 50 and older with Type 2 diabetes with CV disease (only 31% of patients) or older patients with 2 or more CV risk factors treated for up to 6.5 years.**
- **Primary outcome was a 3 point MACE (CV death, non-fatal MI and non-fatal stroke)**
- The Rewind Trial was **completed July 2018 and Lilly announced the top-line results on Nov 5, 2018. The results will presented at the June 2019 ADA Meeting.**

Top-Line Results of Rewind Trial with Dulaglutide

- **"Dulaglutide 1.5 mg weekly significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke**, meeting the primary efficacy objective in the precedent-setting REWIND trial. Eli Lilly and Company's (NYSE: LLY) once-weekly dulaglutide is the first type 2 diabetes medicine to demonstrate superiority in the reduction of MACE events in a clinical trial that included a majority of participants who did not have established CV disease."
- **"REWIND had a median follow-up period of more than 5 years, the longest for a CV outcome trial in the GLP-1 receptor agonist class.** In comparison, other CV outcome trials had more people with a higher baseline A1C and a greater percentage of patients who had established CV disease. **Of the 9,901 REWIND participants, the mean baseline A1C was relatively lower at 7.3 percent, and only 31 percent had established CV disease."**
  - https://www.prnewswire.com/news-releases/trulicity-dulaglutide-demonstrates-

FDA Drug Safety Communication - Risk of Heart Failure (4/5/2016)

- **An FDA safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease.** As a result, FDA is adding new warnings to the drug labels about this safety issue.
- **RECOMMENDATION: Health care professionals should consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure and monitor their diabetes control**. If a patient's blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.
- **Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:**
  - **Unusual shortness of breath during daily activities**
  - **Trouble breathing when lying down**
  - **Tiredness, weakness, or fatigue**
  - **Weight gain with swelling in the ankles, feet, legs, or stomach**

CARMELINA Linagliptin CV Outcome Trial

- **Randomized, placebo-controlled, multicenter noninferiority trial** conducted from August 2013 to August 2016 at 605 clinic sites in 27 countries among **6979 adults with type 2 diabetes, hemoglobin A1c of 6.5% to 10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria).** Participants with end-stage renal disease (ESRD) were excluded. **Followed up for a median 2.2 years.**
- Interventions Patients were **randomized to receive linagliptin, 5 mg once daily (n = 3494), or placebo once daily (n = 3485)** added to usual care.
- **Primary outcome was time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke**. **Secondary outcome** was time to first occurrence of adjudicated **death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline.**
  - JAMA. 2019;321(1):69-79

JAMA Network

From: **Effect of Linagliptin vs Placebo on Major Cardiovascular Events in 6979 Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial**
JAMA. 2019;321(1):69-79. doi:10.1001/jama.2018.18269

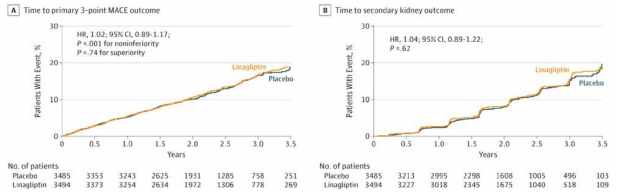


Figure Legend:

Time to Primary and Secondary OutcomesHazard ratio (HR) based on Cox regression analyses in patients treated with at least 1 dose of study drug. A, Time to 3-point major adverse cardiovascular event (MACE) primary outcome (first cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). Median observation time was 2.1 (interquartile range [IQR], 1.5-2.9) years for linagliptin and 2.1 (IQR, 1.5-2.8) years for placebo. B, Time to secondary kidney outcome (first sustained end-stage renal disease, death due to renal failure, or sustained decrease of ≥40% in estimated glomerular filtration rate from baseline). Median observation time was 1.9 (IQR, 1.2-2.6) years for linagliptin and 1.7 (IQR, 1.2-2.5) years for placebo.

FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- **8-28-15 FDA is warning that the type 2 diabetes medicines sitagliptin, saxagliptin, linagliptin, and alogliptin may cause joint pain that can be severe and disabling.**
- The **FDA found 33 patients and all experienced arthralgia that resulted in a substantial reduction in their prior level of activity, including 10 patients who were hospitalized due to disabling joint pain.**

FDA Safety Alert: DPP-4 Inhibitors and Potential for Severe Joint Pain

- In **22 cases, symptoms appeared within 1 month of initiation of treatment with a DPP-4 inhibitor. In 20 of the 33 cases**, the DPP-4 inhibitor was suspected as a possible cause of arthralgia and was discontinued within a month following the onset of symptoms. However, 8 of the remaining 13 cases reported a period of 44 days to 1 year between the onset of symptoms and discontinuation of the DPP-4 inhibitor. In 23 of the 33 cases, symptoms resolved less than 1 month after discontinuation of the drug.
  - **eight of the 33 cases documented a positive rechallenge with the same or other drug in the class**

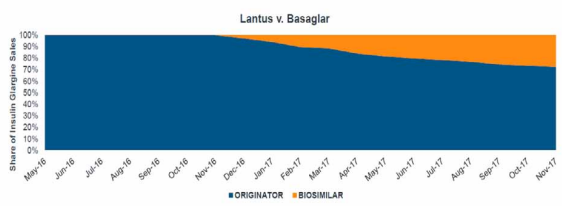
Insulin Glargine – Basaglar by Lilly and BI

- **Dec 16, 2015 FDA approved Basaglar (insulin glargine) but not launched until after Dec 2016 based upon court action. T**he first insulin product approved through an abbreviated approval pathway under the FDA 505(b) (2) application which did rely partly on the safety and effectiveness of Lantus (insulin glargine by Sanofi).
- **Cost: ~$ 343.00 / 5 pens**
- **Lantus SoloStar ~$403.00 / 5 pens ~15% lower than Lantus**

The FDA determined that Basaglar was sufficiently similar to Lantus and in addition Basaglar was studied in two large trials (543 Type 1 and 744 Type 2 patients with diabetes). Like Lantus FDA approved for patients age 6 and up.

Basaglar is considered a "follow-on" NOT FDA approved as a "Biosimilar" product. (There is no reference listed drug for Lantus under the Public Health Services Act)
CVS/Caremark is now excluding Lantus as of 2017

Basaglar is taking Market Share from Lantus



Molecule	Class	2015	2016	YTD NOV 2017
Insulin Glargine	Originator (*Lantus*)	$3,761,997,359	$3,242,925,104	$2,389,475,051
		100.0%	99.7%	81.1%
	Biosimilar (*Basaglar*)	$0	$8,925,988	$558,113,256
		0.0%	0.3%	18.9%

Source: IQVIA, National Sales Perspectives, January 2018

IQVIA

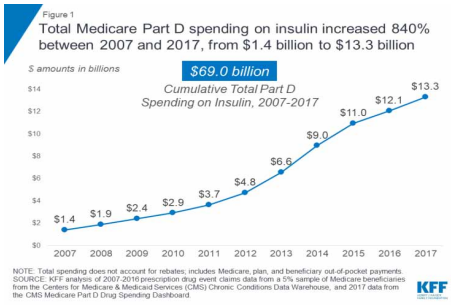
Lilly Announces Lower Cost Insulin Lispro

- Eli Lilly and Company has announced plans to sell Insulin Lispro, an authorized generic version of its brand-name Humalog insulin drug. **Except for the label, an "authorized generic" version of Humalog will be identical to the brand-name insulin drug and manufactured at the same facilities.**
- **Compared to Humalog, Insulin Lispro prices will reduce out-of-pocket costs by more than 50%, with one 10mL vial listed at $137.35 vs. ~$289.00, and a five-pack of KwikPens at $265.20 vs. ~ $550.00. The drug will be sold through Lilly subsidiary ImClone systems.**
- **4/26/2019 BioCentury reported that Express Scripts Holding Co. excluded Eli Lilly's Humalog (insulin lispro) "from its 2019 formulary." The article suggests that the move by Express Scripts supports the notion "that PBMs want bigger rebates, not cheaper drugs."**

Insulin Lispro Brand vs. Generic

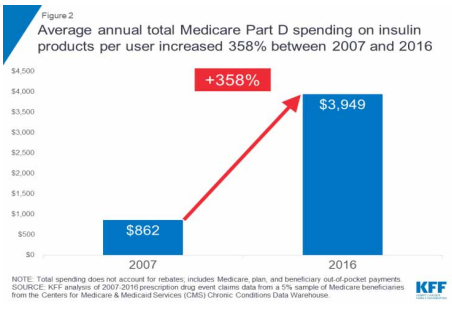
Follow the steps below to ensure that Humalog patients get the most affordable Lilly rapid-acting insulin option: KwikPen example:
1. Run the Humalog KwikPen® NDC (0002-8799-59) to determine out-of-pocket costs.
2. Run the Insulin Lispro KwikPen NDC (66733-822-59) to determine out-of-pocket costs.
3. Compare out-of-pocket costs for Insulin Lispro and Humalog.
4.Because Lilly's Insulin Lispro is a generic, no extra steps or phone calls are necessary to make a switch between products.

How Much Does Medicare Spend on Insulin?



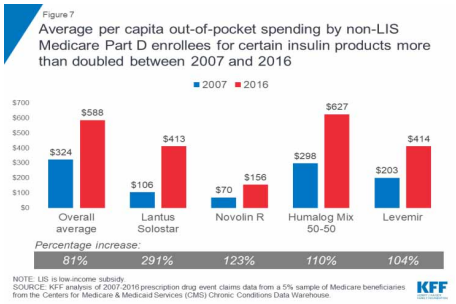
The total number of Part D enrollees using any insulin therapy nearly doubled between 2007 and 2016, from 1.6 million enrollees to 3.1 million—a much smaller increase in percentage terms (86%) than the percent increase in total Part D spending on insulin over the 2007-2016 period (753%)
Kaiser Family Foundation 4-2-2019

How Much Does Medicare Spend on Insulin?



Kaiser Family Foundation 4-2-2019

How Much Does Medicare Spend on Insulin?



Kaiser Family Foundation 4-2-2019

SELF EVALUATION

Evidence-Based Management of Patients with Type 2 Diabetes

1. T/F - The treatment approach to type 2 diabetes should begin with an assessment of cardiovascular disease (CVD) status, other comorbidities, and patient preferences, according to the 2018 joint consensus statement from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD).

2. T/F - In addition to diet and exercise for the prevention of Type 2 diabetes, metformin should be considered in those with prediabetes, especially for those with BMI >35 kg/m2, those aged < 60 years, and women with prior gestational diabetes mellitus.

3. T/F - According to the American Diabetes Association (ADA); Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin.

4. T/F - According to the American Diabetes Association (ADA); patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists glucagon-like peptide 1 receptor agonist is preferred.

5. According to a recent FDA Box Warning concerning increased risk of lower extremity amputations in patients with the following risk factors: in the patient's history that may predispose them to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. The Box Warning is for which medications?

a. Liraglutide (Victoza)
b. Canagliflozin (Invokana)
c. Pioglitazone (Actos)
d. Metformin
e. None of the above

6. What medication was demonstrated to reduce a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2) when added to either an ACE inhibitor or angiotensin receptor blocker (ARB) in patients with Type 2 diabetes and reduced renal function with albuminuria in the Credence Trial?

a. Liraglutide (Victoza)
b. Dulaglutide (Trulicity)
c. Empagliflozin (Jardiance)
d. Canagliflozin (Invokana)
e. Dapagliflozin (Farxiga)

7. According to the American Diabetes Association (ADA) Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium–glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit are recommended as part of the antihyperglycemic regimen. Which of the following medications does not have demonstrated cardiovascular disease benefit?

a. Liraglutide (Victoza)
b. Empagliflozin (Jardiance)
c. Canagliflozin (Invokana)
d. Lixisenatide (Adlyxin)
e. None of the above (all have CV benefit demonstrated)

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

Elizabeth W Woodcock, MBA, FACMPE, CPC

Elizabeth W Woodcock, MBA, FACMPE, CPC, of Atlanta, Georgia, received her bachelor's degree, summa cum laude, from Duke University, and earned an MBA from The Wharton School of Business at University of Pennsylvania. She has worked professionally in the healthcare management field for over 25 years and is a nationally renowned speaker, consultant and author. Ms. Woodcock is a principal of Woodcock & Walker Consulting and has written dozens of books, chapters, articles and white papers including *The Physician Billing Process: Avoiding Potholes in the Road to Getting Paid: Third Edition, 2015*, and *Mastering Patient Flow to Increase Efficiency and Earnings: Fourth Edition, 2017*.

You may contact Ms. Woodcock with your questions and comments at 404-373-6195, or by email at Elizabeth@ElizabethWoodcock.com.

woodcock & associates
CHANGING THE WAY YOU WORK

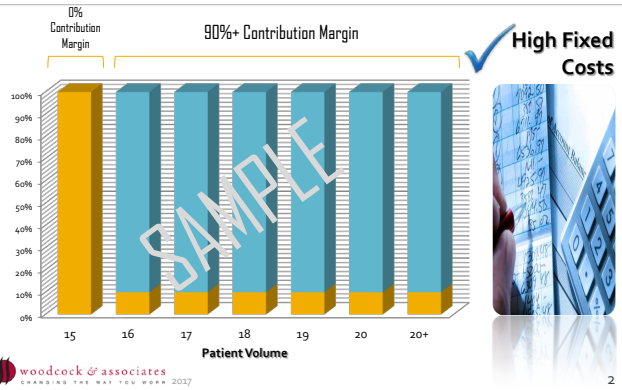
Optimizing Patient Appointment Scheduling and the Bottom Line

Elizabeth W. Woodcock, MBA, FACMPE, CPC

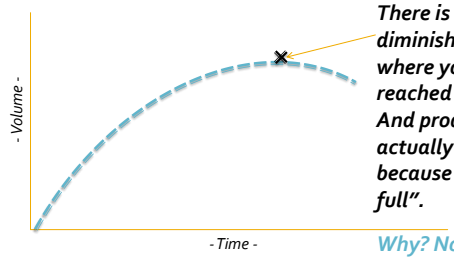
Agenda

- Call to Action
- Key Performance Indicators
- Scheduling Tips
- Patient No-Shows
- Conclusion
- Q&A

Call to Action



Call to Action



There is a point of diminishing returns, where you have reached capacity… And productivity actually starts to drop because you are "too full".

Why? No-shows reduce revenue; burden of deflecting demand increases costs.

Call to Action

Every Appointment is "New Business"

Aren't your schedulers really "sales representatives"?

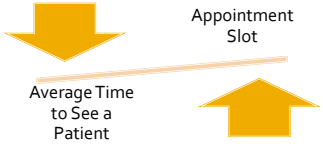
Two goals of scheduling appointments

(1) Capture patient demand (their business)

(2) Perform the function in the most efficient way possible (to get to the next patient!)

Call to Action

- No "right" way to schedule



New	Established
20	10
30	15
40	20

Most common durations

Call to Action

Don't *celebrate* when the patient doesn't show!

Call to Action

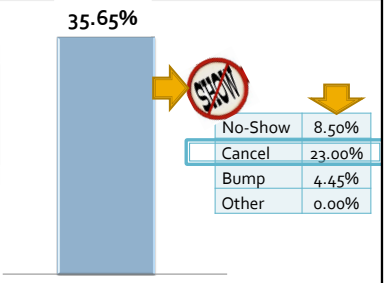
Managing it means more work for everyone involved!

Key Performance Indicators

Dashboard: Patient Flow KPIs

- Missed Appointment Rate (Scheduled but Not Arrived Rate)
  - By Reason: No-show, Bump and Cancel
- New Patient Lag Time
- Established Patient Lag Time
  - By Type
- New Patient Appointments as a Percentage of Total Appointments
- Cancellation Conversion Rate
- Inbound Telephone Calls per Appointment
  - Repeat calls

Key Performance Indicators



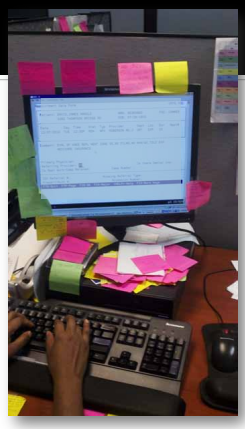
No-Show	8.50%
Cancel	23.00%
Bump	4.45%
Other	0.00%

Source: 2015 Patient Access Benchmark Survey, median. Data may not sum because medians reported. ©Patient Access Symposium® 2016. All rights reserved.

Scheduling Tips

Challenge? Templates are so complex that …

- Schedulers can't schedule – or cost of rework very high
- Productivity is actually constrained because slots go unfilled
- "Search" function becomes *dys*functional



Scheduling Tips

Down to 3 or 4 "standard" types

8:45	Short
9:00	Long
9:15	Short
9:30	Short
9:45	Short
10:00	New
10:15	Short
10:30	Short
10:45	Short
11:00	Procedure
11:15	
11:30	
11:45	Short

Established Pt

Don't let your template *constrain* your productivity!

[Develop standard template for new providers]

Scheduling Tips

Never schedule a new patient at the top of the morning or afternoon clinic

If you have multiple physicians, always stagger start times!

Scheduling Tips

- Should I double-book? YES *Strategic* **Overbooking**

1. Use based on required resources
   Ex.: Patient scheduled for in-office procedure; needs to be prepped by nurse. Established patient with acute problem – 15 minutes is scheduled at same time. When established patient is done, procedure patient is ready!
2. Depends on your no-show/cancel rate; aim for slightly lower than the actual rate (e.g., 10% of slots if 14% no-show rate)

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Scheduling Tips

- Should I double-book? YES *Strategic* **Overbooking**

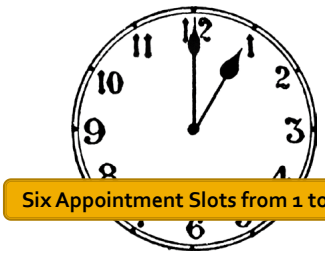
3. Double-book certain highly-probable no-show slots
   Ex.: ED F/U + Uninsured
   Ex.: Patient with two no-shows in past 90 days
   Ex.: Disconnected phone # (when confirmation call

10 a.m. + 2 p.m.

 ED F/U = Emergency Department Follow-up 17

Scheduling Tips

- Five-Minute Clinic



Six Appointment Slots from 1 to 2 p.m.

 15

Patient No-Shows

- Engage Your Patients

 16

Patient No-Shows

- Make an appointment *with* the patient, not *for* the patient

FORBIDDEN Auto-Booking

 21

Patient No-Shows

Or, better yet, let the patient do it him/herself

Result?
Cut your No-Shows in Half – and Reduce Staff Involvement

 22

Patient No-Shows

"Self-Scheduling?"

Request — Patients make the request online, but you call to actually schedule

CHAT

Direct — Established patients book their own appointments

Open — New patients book their own appointments

Commonly through the platform of an external vendor

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Patient No-Shows

- Appointment confirmations
  - Phone Call – Automated and Warm
  - Text (Opt-out)*
  - If booked > six months ago, call 2+ weeks in advance

Work the non-delivery/ cancellation report!

*"We grant the exemption [for] … calls … that have a healthcare treatment purpose, specifically: appointment and exam confirmations and reminders…"
Telephone Consumer Protection Act (TCPA), 2015

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Patient No-Shows

- Make it Easy To Cancel

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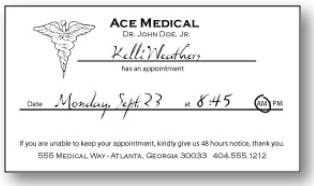
Patient No-Shows

- Refine the return-to-office process



At 12 weeks, recall don't appoint

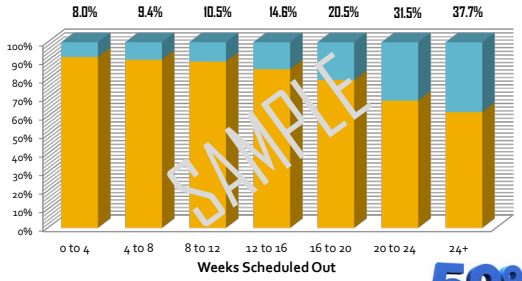
…find the "right" scheduling horizon by analyzing your own data

22

Patient No-Shows

Why *Recall*?

Evaluate Your Scheduled But Not Arrived Rate



12 months… 50%

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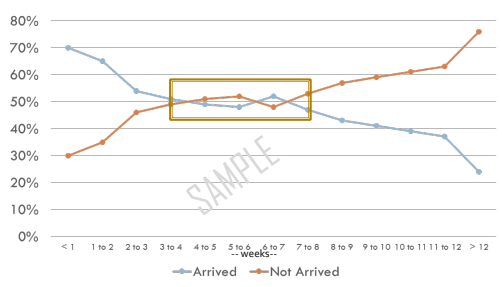
Patient No-Shows

New Patient Appointment Status by Lag Time



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Patient No-Shows

The Monday Mentality

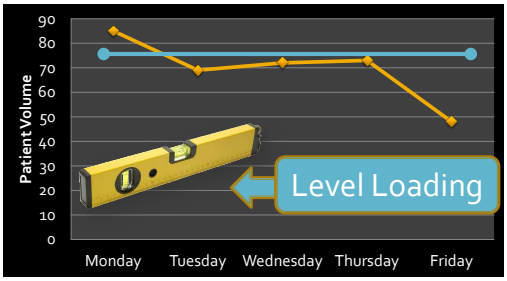
"Elizabeth, if you'd only been here on a Monday, you would have seen how hard we really work…"

Do <u>not</u> schedule routine follow-up visits on a Monday

Level Loading is a Key Scheduling Strategy

25

Patient No-Shows



26

Patient No-Shows

- Maintain a wait list

Name	MRN	Cell#	Appt
Jones, Mary	4593982	706.830.1393	May 12
Howards, Stanley	4905091	404.394.5241	June 1
Walker, Heather	4092015	404.830.1054	June 14
Shaw, Lauren	4030190	706.893.1043	June 16
Pitt, Karen	4010308	912.813.5101	June 16

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Patient No-Shows

1. If a large practice, on a health system campus or employed by a health system, keep a wait list of employees
2. Maintain a list of patients who need services (e.g., Medicare Annual Wellness Visit)
3. Automate the waitlist/backfill process

32

Patient No-Shows

- Always check on patients' future appointment(s) if booking for an acute reason

29

Patient No-Shows

Afternoon "Sweep"

- **What does tomorrow look like?**
- **Where are the holes?**
- **FILL THEM!!!**

34

Patient No-Shows

- Document, document, document
  - Consult with your malpractice carrier
- Call and reschedule (and document)
  - "Dr. Jones wanted me to call you.. "
  - "Is everything okay…?"

Patient No-Shows

```
Schedule an Appointment                                   USAC.ONE

   Patient:                    MRN                    CC: N
  Provider:                    DOB:
Department:                    Special Needs:         NPP:
     C/T/D:                    FSC 1:
Visit Type:                    FSC 2:
 From Date:                    Demographics Valid Thru:
   APE/DOW:                    Fam MD:
  Location:
                                ** Noshows: 1 **
    Search
    Option:   SU   First Available  Summary  Quick Summary  Reminder

Press <Return> to continue
```

Track History of No-Shows: "CNS1", "CNS2", "CNS3"

Patient No-Shows

- Create another template: "Dr. No Show"

	Dr. Scott	Dr. Rego	Dr. Martin	Dr No Show
8:00 AM	Patient Jacob (508) 717-4968			Patient Dustin (774) 202-1234
8:20 AM		Patient Nancy (508) 999-1234		
8:40 AM	Patient Sheila (508) 996-0935		Patient Mary (508) 555-4444	Patient Robert (508) 123-9876
9:00 AM				
9:20 AM		Patient John (617) 345-6789		
9:40 AM	Patient Carrie (508) 717-5300			
10:00 AM				

- Put CNS2, CNS3 on this "schedule"
  - Perhaps add the other predictable no-shows
- Set appropriate expectations with patients

Patient No-Shows

- Charge a penalty

Cons	Pros
Drive patient away	Drive patient away (??)
Bad PR, particularly if your practice is dysfunctional	Change patient's behavior (maybe…)
Cost you money	
Rarely get a response (or $)	
Medicaid plans won't allow it	

- Consider:
  - Charge second-time offenders only
  - Require pre-payment to "hold" the slot

Patient No-Shows

- In October 2007, CMS gave the green light to charge Medicare patients

"CMS policy allows physicians…to charge Medicare beneficiaries for missed appointments, provided that they do not discriminate against Medicare beneficiaries but also charge non-Medicare patients for missed appointments and the charges for Medicare and non-Medicare patient are the same. The charge for a missed appointment is not a charge for a service itself…but rather is a charge for a missed business opportunity."

www.cms.hhs.gov/MLNMattersArticles/downloads/MM5613.pdf

Patient No-Shows

- Dismiss?
  - Consult with your malpractice carrier for patients who miss multiple appointments
    - Include their recommendation for *how* you communicate with the patient

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SELF EVALUATION

Optimizing Patient Appointment Scheduling and the Bottom Line

1. T/F - Celebrating when a patient doesn't show up may result in a *future* no-show, as patients perceive that they are actually doing you a favor by *not* presenting for their appointment.

2. Support a positive cultural shift to embrace patient access by asking physicians to say this to the entire team:
   a. "It's so much better when the patients fail to show. . . "
   b. "Thank you for a *full* day…"
   c. "Please create holes in my schedule so I can tend to emails and personal errands. . . "
   d. "Bring your lunch and work during your breaks so we can spend more time on patients. . . "

3. A practice in preventing no-shows is to communicate to patients:
   a. Come half an hour early to fill out paperwork
   b. Bring in their parking pass so you can validate their parking
   c. The appointment is reserved for you, and another patient may not get the care he or she needs if the patient fails to show
   d. Refer at least three friends and receive a free office visit

4. T/F - Reviewing the *future* appointments scheduled for patients is important for employees involved in the scheduling process, particularly in the event of a patient booking an appointment for an acute issue.

5. To determine an effective dismissal protocol, consult with your malpractice carrier to discuss terminating your relationship with _____ who miss multiple appointments.
   a. Schedulers
   b. Staff
   c. Providers
   d. Patients

6. Don't schedule _____ patients at the top of the morning or afternoon clinics.
   a. Surgical
   b. Female
   c. New
   d. Frustrated

7. To smooth out supply and demand across the week, avoid scheduling routine follow-up visits on what day of the week?
   a. Monday
   b. Tuesday
   c. Wednesday
   d. Thursday
   e. Friday

8. Maintain a _____ of patients to fill last-minute cancellations.
   a. Waitlist
   b. Pile
   c. Immunization spreadsheet
   d. Recall posting list

9. At a certain point in time – referred to as your scheduling _____, it is actually more efficient to recall patients than appoint them into a particular slot.
   a. Cloud
   b. Horizon
   c. Computer
   d. Daily protocol

10. Level _____ is the term to describe smoothing out patient demand across the week so that your capacity can be most effectively and efficiently used to manage it.
   a. Headedness
   b. Communication channel
   c. Loading
   d. Stations

11. T/F - There is a "tipping point" of diminishing returns, where you reach capacity – and your productivity actually decreases as a result of patient no-shows and the burden of deflecting this excess demand.

Answer Key: 1. T, 2. B, 3. C, 4. T, 5. D, 6. C, 7. A, 8. A, 9. B, 10. C, 11. T

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Ike Z. Devji, Esq., of Phoenix, Arizona, has been solely focused on asset protection and wealth preservation planning for the last 14 years. He and his colleagues have protected over $5 billion in personal assets for a national client base that includes thousands of successful physicians, as well as business owners and entrepreneurs. Mr. Devji is a noted national educator (CME, CLE, and CE), an author with over 300 nationally published bylines, and a frequent speaker, having taught thousands of doctors, lawyers, and advisors on asset protection and risk management, in addition to being a contributing author to multiple books and a dozen medical journals. He is AVVO rated "10.0 Superb" for nine years in a row and is included in "Arizona's Finest Lawyers" among other distinctions.

You may contact Mr. Devji with any questions or comments at (602) 808–5540, by email at id@thewealthy100.com, or through his website at www.ProAssetProtection.com.

Protecting Against Legal and Financial Risk - A Checklist

Following is the most basic "must have" checklist of legal and financial planning that can help physicians to run their businesses in a safe and predictable way. Many common exposures can be eliminated or well limited by working with top counsel to identify and manage these risks now, while you have the legal right and financial ability to do so.

No list of this nature can ever be a complete, fact specific summary of all your risks. It is a good starting point that can help you protect your success with some broadly applicable basics you may be missing completely or need to update.

1. **Asset Protection Planning.** Think of it as **Net Worth Insurance**, managing risks, legally organizing and segregating your assets and protecting them from your unrelated personal and professional liability. Key issues every plan should address:

    - **It is always proactive.** Planning must be done before any problem occurs, acting late is not only ineffective, it is often illegal and both civilly and criminally actionable
    - **It is not covered by your revocable living trust.** Your traditional estate plan alone, though necessary, does not protect your assets, from your liabilities, during your life
    - **It is a system of layers.** These layers include insurance, legal tools and enforced compliance measures
    - **It seeks to manage risk instead of crisis.** Good plans try to limit or eliminate common identifiable risks and keep you out of trouble in the first place.

    Have It _____ Need It_____ Don't Know _____

2. **Coordinated Financial Planning.** A good financial advisor can help make sure the money you make is working as hard for you as you worked for it and that the investment planning you have in place includes **both growth and loss prevention** strategies that address the very real scenario of a down market. Those who planned only for an upside economy took many years to recover from the 2008 crash. I look over the shoulders of some of the most successful doctors in America and I can tell you that there is huge difference in the wealth accumulation levels between those who "work as hard as they can and spend as little as possible" and those that have a specific goal, a plan to get to that goal and the right help. You're a DIY type that thinks you can do as good or better (cheaper, let's be honest) than an advisor? Great, get educated and consider paying a planner once for a customized plan that you can use as a guide.

    Some key issues to address in a comprehensive financial plan:

    - Retirement income funding
    - Education plan funding -Investment management -Disability, long term care, critical care funding

    Have It _____ Need It_____ Don't Know _____

3. **Disability Insurance (all 3 kinds).** This commonly overlooked tool protects your personal income cash flow against your own injury and illness, the times you need it the most. Large amounts of coverage with lots of sophisticated bells and whistles are available. The beginning of the year is a great time make sure that your **cross-purchase or buy-sell agreements are properly funded.** If your partner has a stroke or some other debilitating illness, how long will you (or she) be willing and able to make large monthly payments to a non-productive partner? If you can't work and earn, how long will your cash reserves last before you are forced to liquidate savings and other assets?

    In addition to personal disability insurance, consider these two additional areas of coverage, especially for

small practices:

Disability Overhead Insurance: Keeps the office open, bills, rent, insurance, taxes, salaries etc. paid so that you actually have a practice to come back to.

Key Person Disability: Covers the loss and replacement of a key employee that is responsible for production, operations, etc.

Have It _____ Need It_____ Don't Know _____

4. **Life insurance** – Make sure you have appropriate amounts to cover estate taxes, **generate income** for survivors and pay off debts you want settled. We also make sure that you are not paying too much and have the most flexible policy with the greatest number of benefits. Again, cross-purchase and buy-sell agreements must be carefully funded. I routinely see these agreements between our business owner clients that are either unfunded or underfunded. If your partner dies with no coverage or inadequate coverage in place you could easily find yourself across from their family in a courtroom explaining why the business should NOT be liquidated to pay them the deceased's share.

   Have It _____ Need It_____ Don't Know _____

5. **Worker's Comp Coverage.** Make sure your employees are protected against on the job injuries and their rising costs and that you are protected against the significant liability for what happens to them. The scope of this **liability has INCREASED** with new risks like active shooters and workplace violence for which practice owners and operators are increasingly personally litigation targets.

   Have It _____ Need It_____ Don't Know _____

6. **Employee Benefits Planning.** From 401K to Executive Compensation planning, there are a number of ways to provide these benefits, and some are more advantageous to you, the business owner, than others. This is also an increasingly important **employee retention strategy.** Many of these programs also have significant legal burdens and compliance risks, so get real help, unless you've been trained to do things like write an investment policy statement for a company 401K yourself. If you and your partners are actually taking on the significant risk of managing a plan yourself, you must also have specialty **insurance to cover your fiduciary liability.**

   Have It _____ Need It_____ Don't Know _____

7. **Employee Handbook and Dispute Resolution Policy.** Governs their rights and your responsibilities, controls actions in the workplace and your employer policy. If you don't define certain polices the courts (or worse your employee's attorneys) will define them for you. This is one of the highest ROI investments you can make in your business in my opinion. **These should be custom drafted, updated and reviewed regularly and should be state specific and uniformly enforced.** Right now the average sexual harassment verdict, as just one example, is $530K. Your business is 5 times more likely to be sued by an employee than for any other reason. Have a plan.

   Have It _____ Need It_____ Don't Know _____

8. **ALL The Right Corporate Formation.** Does your corporate formation (or lack of it) expose you and your personal wealth to liability and taxes? Will it hinder you in the case of sale? Do you have too many eggs in one basket? For example, if your business or medical practice entity also owns the building it operates from you are needlessly exposing the real estate asset to unrelated professional liability. Simple fixes can save you millions if something bad happens. These documents should be reviewed and updated periodically as well.

   Have It _____ Need It_____ Don't Know _____

9. **Professional Accounting Service.** A top-notch CPA? Taxes and payroll are just the beginning; you need a professional

who proactively offers solutions and shows you legal tax avoidance options in addition to the administrative and reporting functions we all rely upon them for. A good CPA calculates what you owe Uncle Sam to the exact dollar whereas a great CPA helps make that number as small as the law allows. They can also help keep you away from the myriad abusive tax schemes that physicians love and are heavily targeted by like abusive captive insurance companies, trust scams and etc.

Have It _____ Need It_____ Don't Know _____

10. **Real Estate Depreciation / Property Tax Reduction Study.** You can often get tax deductions for R.E. depreciation NOW when you need them, not just 30 years from now with professional help. Most of my clients own significant real estate and we see this as money left on the table time and time again. We also see that many R.E. owners are paying tax rates on their property that is higher than it should be and often suggest reviewing the tax rate with a qualified professional. This applies to both your practice facility and other investment R.E. you may own, like an ASC, commercial property, apartment building, etc.

    Have It _____ Need It_____ Don't Know _____

11. **FULLY FUNDED Buy-Sell Agreements.** Any business or medical practice with multiple owners must have a funded buy-sell agreement in place to protect the partners and their families from the death or exit of a partner. If you do have an agreement, see that it is actually **adequately funded with life, disability, disability buy-out, and any other insurance required** and that the insurance limits are reviewed every year or two and kept adequate to meet the **valuation** your buy-sell specifies. **75 percent** of the agreements we see are outdated, underfunded, or unfunded. Finally make sure the agreement is wide enough in coverage to include all the **"Five D's": Death, Disability, Divorce, Departure and Disqualification.**

    Have It _____ Need It_____ Don't Know _____

12. **Estate Planning.** What happens to your family and the fruits of your life's efforts at your passing? Should they get the assets outright or should they be held in trust? How will the assets be protected from your heirs' own liabilities including their spouses and even possible bankruptcy? How can we avoid a fight over assets and protect those we leave behind? These are just a few of the issues that every well drafted estate plan will help address. For most high-income professionals like doctors, the appropriate estate plan starts with a revocable living trust "package" that includes, wills, living wills, healthcare and financial powers of attorney and other vital documents.

    Have It _____ Need It_____ Don't Know _____

13. **Exit Plan Strategy a.k.a. Succession Planning.** Ok you've been successful at what you do – now what happens? Make sure your business is an asset when you are ready to sell it or retire and that the planning you have done minimizes your tax exposures on the sale or transfer. A little proactive work here can save you as much as 50% in taxes and help make sure that your legacy and this valuable asset is handled with the respect and care your efforts deserve. This can include selling it or passing it on to family or key employees and also requires that we address your asset protection planning. Remember, you are trading an income producing asset for a finite lump sum of money or stream of payments that needs to be protected from a variety of exposures, including the buyers themselves.

    Have It _____ Need It_____ Don't Know _____

14. **Long Term Care Insurance.** Aging and its costs are an inevitable expense as medical technology progresses. Those who handle the costs and their future needs proactively fare far better than those who do not. A full 40% of American bankruptcies result from medical bills and these costs are growing yearly by leaps and bounds. Any retirement plan strategy MUST account for these costs.

    Have It _____ Need It_____ Don't Know _____

15. **A Security Program.** These programs fall into two primary groups designed to deter, detect, report and react to various threats. First are **active security measures** like guards, metal detectors and other mandatory electronic screening. Second are **passive security measures** including:

    Locked doors with limited and controlled pedestrian access;
    Controlled vehicle access including active and passive barriers;
    Various electronic access controls like key cards and biometric scanners;
    Electronic monitoring systems like cameras;
    Lighting, Landscape and Architecture controls.

I'm also encouraging medical practice owners and operators to implement **two additional safeguards based on the now common reality of workplace violence and active shooters** by implementing the following:

    A **weapon policy** at your practice including both **internal policy** on who in the office has a gun and **external policy** on the ability of patients and visitors to have a firearm at your place of business;
    Active Shooter Insurance that covers your business, employees, patients and third parties.

The way these cases are playing out, there may be liability for failing to act in any of these areas, despite not having any specific legal duty to do so.

16. **A Comprehensive Liability Insurance <u>Program</u>.** Insurance is a system of layers that creates layers of coverage to protect you from predictable risks, not just a single policy. It's vital that you understand the details of your insurance policies and that your work with an experienced, multiline commercial insurance broker that can give you coverage advice, not just sell you a policy.

What The Insured Must Know About Their Own Coverage

1. Are coverage limits adequate for current values and threats?
2. Are policy limits shared between different areas of coverage?
3. Is the scope of the coverage adequate for current threats?
4. Is the policy drafted reasonably in terms of exclusions?
5. Is this policy "defense inside the limits"?

Using Layers of Specialty Liability Insurance, A Few Common Examples

*Risk Management With Liability Insurance, How Many Layer Are **You** Missing?*

1. *EPLI - Employee Lawsuit Exposure - external and internal*
2. *D&O - Directors and Officer's*
3. *Data Breach and Cyber Liability*
4. *Worker's Comp Insurance*
5. *Professional liability Insurance (i.e. malpractice, E&O, etc.)*
6. *RAC Audit Insurance*
7. *Personal liability Insurance with seven figure umbrella (home and auto)*
8. *<u>Adequate</u> general business loss and liability coverage*

Directors and Officers Coverage: D&O

- Side A: For the individual director and officer
- Side B: For corporations and their balance sheets if they are contractually obligated to indemnify their directors and officers for a suit.
- Side C: For security claims

Exposures for Privately Owned Companies

- Outside advisers to management
- Domination by a small group of shareholders
- Limited time of commitment by directors
- Claims by third parties

-Alleged trade secrets were stolen

-Not delivering goods on time as told by the president of their company

-President and Vice President held liable for a corporation's illegal dumping

Employment Practices Liability Insurance -EPLI

• Protects management against suits from employees

- Discrimination
- Wrongful failure to promote
- Wrongful failure to employ
- Wrongful termination
- Sexual harassment
- Retaliation
- Defamation
- Invasion of privacy
- Fraud
- Negligence

CYBER LIABILITY OR DATA BREACH COVERAGE

• What is Cyber Liability?

- Started as a professional liability for companies that had hardware and software services.
- Today it has expanded to cover third party claims but has still maintained the same name.

– Same professional insurance coverage as when started

– Privacy Liability

- **Covers loss of personal identifiable employee and customer information**

– Security Liability

- **Covers failure to prevent hacker or viruses**

– Website Media Liability

- **Covers libel, slander, and copyright infringement from your website content**
- **First Party Cyber Extortion**
- **Covers expenses to respond to a threat to harm or release your data as well as cover ransom payments if necessary.**

First Party Privacy Breach Response

- Customer notification expense
- Credit monitoring expense
- Computer and legal forensic expense
- Credit and identity repair expense
- First Party Business Interruption and Data Recovery Extra Expense
- Regulatory Defense and Penalty

RAC AUDIT INSURANCE is For ANYONE that bills insurance

Who do RAC Audits Affect?

- Almost any healthcare provider (including hospitals, doctors' offices, home health care providers, nursing homes, or anyone else who submits bills to government programs such as Medicaid or Medicare) should prepare to be audited at some point.

What are the Risks and Burdens of a RAC Audit?

- The auditors themselves work on a contingency fee basis and the five regional firms contracted by the government are paid up to 12.5% of all claims they successfully identify as invalid and which they collect. The burden this place on healthcare providers from both a resource, financial liability and record keeping standpoint is significant. Auditors can go back as far as three years and can request 400 files every 45 days, a significant defense burden for practice owners.

A good policy may also cover expensive related exposures like:

- Medicare & Medicaid Audit (RAC Audit)
- Commercial Payor Audits
- STARK Violations
- HIPPA Compliance
- EMTALA Violations

Workplace Violence and Active Shooter Insurance

The last one month alone illustrates the wide range of threats all American business owners and their counsel must be prepared for. This is only a **partial list** of events involving workplace violence and active shooters.

1. North Carolina University Shooter
2. Poway Synagogue Shooter
3. San Francisco Pedestrian Vehicular Assault
4. Christ church Mosque Shooter
5. Multiple Foiled School Shootings

Who is at Risk?

This is a rapidly expanding area of liability for all business owners and real estate owners, managers and employers in particular. Both active security and compliance programs and high limits of specialty liability insurance need to be part of any competent asset protection plan.

Sample At Risk Individuals:

- Real estate owners and Facility Operators
- Executives of corporate entities with liability
- Employers

At Risk Locations? EVERYWHERE

- Public facilities like concert venues, bars, clubs and sports arenas
- Schools
- Religious Institutions
- Office, Apartment and Hotel Properties
- Retail
- Healthcare facilities

What <u>Can Be</u> Covered by Active Shooter Insurance?

- Physical Damage -Including repair, relocation and teardown
- Legal Liability and Litigation Defense

- Crisis management
- Business Interruption Coverage
- Medical Expenses, funeral expenses and death benefit
- Loss of attraction

Watch for exclusions that can make a policy nearly WORTHLESS

Again, Expert Advice on Specific Policy Details is Vital

1. Terrorism Exclusion (Have You Seen the News?)
2. Casualty Threshold Limits (Sorry, only two people killed)
3. Employee Exclusions
4. Vehicle Exclusions
5. Mental Anguish Exclusions
6. Domestic Violence Exclusions (30% of all workplace violence!)

Why would someone buy a policy with such ridiculous exclusions? THEY WOULDN'T if they actually knew what they were buying or were well advised.

TYPE	HAVE IT	NEED IT	DON'T KNOW	COVERAGE LIMIT
EPLI				
CYBER				
D&O				
MALPRACTICE				
RAC AUDIT				
WORKERS COMP				
ACTIVE SHOOTER				
GENERAL LOSS & LIABILTY				
PERSONAL UMBRELLA				

SELF EVALUATION

Protecting Against Legal and Financial Risk - A Checklist

1. T/F - My medical malpractice policy adequately protects me against most business risks.

2. T/F - Re-titling my home into my family trust protects its equity from professional risk.

3. Cyber Liability Insurance can protect you against which of the following risks?

a. Employee theft of PII and HIPAA info
b. Third party hacking or theft of Patient PII and HIPAA info
c. Ransom-wear attacks that lock up all your data
d. Defense costs for a breach
e. All of the above
f. B and C Only

4. Disability insurance can replace which of the following?

a. Your personal income
b. Your business income adequate to cover practice expenses
c. Income lost by the disability of a key employee
d. All of the above
e. A only

5. T/F - I don't need active shooter insurance because I have an umbrella policy and a no-firearms policy at my business.

6. T/F - Medical practice owners cannot be held liable for random acts of criminal violence committed by third parties.

7. Medical Practice owners and operators can be held liable for which of the following after an act of workplace violence:

a. Injuries to patients only
b. Injures to patients and employees
c. Acts or omissions that contributed to the injury
d. A and B only
e. A, B and C

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

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Understanding and Safeguarding Against Practice Embezzlement

This Session

- Analyze The Financial Work Process
- Recognize Areas Of Financial Risk In Your Practice
- Physician's Actions That Support Internal Controls
- Hiring Practices With Security In Mind

Objectives

(10%) of the nation's healthcare cost is lost through fraud

- We are not exempt from these incidences and are increasing at an alarming rate.
- It is projected during a five (5) year period of time; over (80%) of medical practices will experience embezzlement in one form or another.
- And of those committing the embezzlement, it is estimated that (70%) have done this before with a previous medical practice.
- Even with great policies in place, we all tend to relax.
- What we forget is that no-one's life is static – as our lives change- so do our needs!
- Throughout the session there will be giving specific examples of experiences other practices have had that may help you prevent this from happening in yours.
- Think of your office and how it may help you and your staff.

Consider Your Office and Opportunity…

One word – opportunity - you will hear this word a lot

For a thief - this is the one thing that makes it all happen.

Each practice is different – No matter the size or how much we trust our staff, we all need to protect our practice.

An example? Jenna was a wonderful front desk receptionist who was always friendly with the patients and a dependable employee.

- Her son became very ill and she began pocketing little bits of cash from the front desk. Nobody noticed. Still needing more money and nobody noticing, there was a patient to pay $200 cash and jenna took it.
- The patient called a month later asking why a bill was received when she had paid?
- We tracked the missing ticket and discovered the discrepancies that supported the patient's claim.
- Although a dependable employee, had to be let go that day.

HOW DOES YOUR OFFICE COMPARE?

With over 50 billion in theft annually…

***most typical scenarios* - let's see if they sound like your practice?**

- Under 100 employees
- average income under $60,000 per year
- 8%-10% is the average percentage of a physician's salary that is typically embezzled

The biggest factor other than opportunity?

- never discount the loyalty factor!
- theft can increase or decrease depending upon the employee's personal loyalty to the physician, practice and patients

Most commonly reported fraud schemes in health care

- skimming cash
- medical billing fraud
- submitting invoices for fictitious goods or services
- theft or misuse of non-cash assets of the organization , supplies, samples, etc
- forging or altering a check on the organization's account or stealing a check legitimately issued to another payee

BUILD A SOLID FOUNDATION- WITH EMBEDDED AND CORE POLICIES

- Almost half of stolen from practices is cash
- It's typically a trusted employee who has been around for years and handed over the entire practice.

Prevention strategies are particularly important to minimize the risk because a business's insurance may not cover the entire loss, which can be significant

- The first step to deter theft is to develop a system of checks and balances.

"The key is to have good financial controls, and people aware they are being watched, For example, the person who collects money at the front desk should not reconcile the books at the end of the day or month. The person who prepares the bank deposit should not be the one who takes the money to the bank.

The division of labor can be difficult– and physicians have to be a part of monitoring.

- For instance, a physician can look at a "dashboard" daily patterns
- 8% of embezzlement are from misuse of noncash assets, establish inventory controls for equipment, Rx pads and drugs.
- About 82% of embezzlers were terminated, but without involving the police.

Who's Really Handling The Money?

- Who is actually handling the money? And access to bank accounts?
- There is so much money," especially from those who have high-deductible plans.
- The risk is especially high at the beginning of the year when everyone is meeting their deductibles!
- You can come back from lunch - someone has gone home and someone else is at c/o with the same cash drawer!!

•These controls do take concerted time and effort with all parties, so yes, there is the cost of "time" involved…… but think of the cost not to.

•If employees know they are monitored, then one of two things will happen…

• They will either be glad they can account for their actions, or move on to greener pastures

•Ensure that each person understands what they are supposed to do, and document procedures for reference are easily accessed.

YOU AND YOUR ACCOUNTANT

- They are ultimately the manager's checks and balances!
- It may be a good idea to have your accountant in on discussions such as contract renewals and other projects that involve projected income along with a capital outlay
- This is one of those times worth hiring a true professional.
- •Story – a paraprofessional- discovered that the manager kept two sets of books and embezzled thousands from a non-profit!!!
- **Lesson? Never allow one employee be in control of all financial transactions.**

YOUR INSURANCE ACCOUNTS RECEIVABLE IS 2/3 OF YOUR INCOME.

•Of course forgo paper when electronic payment is an option

•Billing company?

One way to track ACH amounts deposited to the money amount applied, is to match the bank deposits to reports from payers and your practice management system.

•Also ask to see detail of write offs

• is someone in your office checking for ACH deposits?

What else do they see? … All of your checking activity?

- Be more than aware of who has access to information and access to money.
- And should be part of your new employee is well as your termination exit check list

- **THE FRONT DESK AND BILLING DEPARTMENT** staff fill completely different roles but a part of the same department and should support each other as such.
- They can be each other's check and balance throughout the day .
- This also serves as a good confirmation of duties at the end of the day as the front desk completes their reports and turning it into billing or other staff to be confirmed and onto the next step

OFF BOOK FRAUD – BEFORE IT HITS THE BOOKS

- If your practice accepts donations please be sure that your system has a patient named "donation" so if anyone would like to remain anonymous , can still run every donation through the system.
- If patient calls for a refund – confirm its validity
- Employees have been known to "work" with patients
- Review patient accounts "on hold" should not be happening
- Remember cash in one's hand equals------ o p p o r t u n i t y!

AND WHAT ABOUT THE PATIENT?

Every national initiative — all involve patient self care

• Your staff continually reminds patients that they have agreed with the insurance company that they would pay their portion of the cost……

When I was a manager I would say that I can administrate any plan as best I can but I cannot change your benefits.

• Healthcare decision making includes financial responsibilities too!

We can help them decide determine the best way to remit for services with as many options as possible

• Choices? A sign posted at the check-in and check-out "Please be sure to get a receipt"

• **Electronic billing and payments = best way to separate the money from the transaction** –reduces opportunity to divert funds.

• Patient portal

Electronic options to help collect money at check-in Kiosk/tablet that accepts payments

AS WE BECOME RELAXED IN OUR EVERY DAY ROUTINES, WE BECOME QUITE VULNERABLE•

• Keep checks in secure place
• No signature stamp – (they are still around!)
• Invoice for every check and all purchases authorized
• Limit max transfers, withdrawals to $5,000 or $10,000

GENERAL CONTROLS - IT'S GOOD TO CONSIDER THE FOLLOWING AREAS OF RISK:

- Are vacations for the individuals in your accounting department required, and does someone else do their job while they are gone?
- Are all employees who handle cash receipts and disbursements bonded, and do you have adequate insurance coverage for employee misconduct?
- Are only authorized individuals given access to the accounting system and general ledger, and are appropriate user names and passwords used?
- Do employees know that physicians and management review daily transactions?
- Do you have a mechanism in place for employees to report suspected fraud anonymously?

- **THINK OF HOW MUCH MONEY YOUR ACCOUTNING STAFF HANDLES EVERY DAY!**
- 100% back up for expense reports and credit cards
- Every staff member should be accountable for each transaction and every penny!

WHAT CAN YOU CENTRALIZE ? ANYTHING YOU PURCHASE FOR SEVERAL PEOPLE…

- **REDUCE PERSONAL ITEMS IN PRACTICE BILLINGS! DRY CLEANING - LAB COATS/SCRUBS, TELEPHONE**
- Separate accounting functions, one person who opens the mail , logs what is received, and the next posts to the system- any staff member that has access to make accounts receivable adjustments (such as patient or insurance write--offs) in the system, offers the opportunity to steal
- If job functions are separate, two or more employees would have to collude for the theft to be concealed, thus reducing opportunity.
- The doctor/lead physician is is the person to approve new vendors. Never the person writing the checks
- **ELECTRONIC BANKING?**… Confirm and verify exactly who has access.

WE TEND TO THINK AND ACT IN SHORT TERM RESULTS

- If that money is just sitting there – why not?
- It's like a piece of chocolate cake – we can only resist so long!
- Sometimes it is a mistake – and the employee realizes that no one notices the money missing!
- So they try again!
- Reduce the risk by shielding the opportunity
- Psychologically– when we diet, and give in just a little and gain weight back – we figure… why not- I have already broken the diet….
- This is not much different

PAYROLL EMBEZZELMENT – THE OPPORTUNITIES ARE ENDLESS!

- **Payroll is not hard but a million details that should be checked off on:**
- Gross payroll, total withholdings, net payroll, and leave time used.
- It is imperative that these amounts be looked at each payroll, knowing the patterns is huge!
- Adding vacation time
- Fake employees
- Bonuses given to certain employees were not authorized by physicians
- **Are pay rates of employees reviewed regularly by owners to determine the accuracy? At least monthly!**
- Is an outside payroll service provider used? Might be a good idea!
- Is there a proper system in place for authorizing pay rate changes and adding new employees into the payroll system?
- Are there procedures in place to ensure payroll tax liabilities and 401(k) withholdings are paid on time?

PETTY CASH – INCIDENTALS ONLY! The occasional pizza additional postage, coffee run.

- Only one person in charge
- Randomly check balance and documentation – make sure nobody is borrowing between reconciliation
- Receipts presented for replenishment

FRONT DESK DRAWER

- Consider a maximum amount of $200
- Drawer is balanced daily – and that balanced to the system
- Smaller amounts of cash are easy to get relaxed about, but remember some people look for those situations
- Reconciles encounter forms to drawer bank and receipts. - Submits tapes too! If warranted

- **COUNT THE CHANGE TOO**! You would be surprised how many people take a lot of change …why? Because they can!
- **IT'S THE LITTLE THINGS THAT COUNT!** Think of medical supplies, cough syrup, formula, coban, bandages, coffee etc.

- **CREDIT CARD ON HOLD** is a wonderful thing that is totally secure in your office as payments are made automatically on a monthly basis or whatever is decided for your office and patients.
- **Lesson?** Credit card on hold is a great thing for checks and balances because information is encrypted, tokenized and processed on your practice management system.
- One of the best things about credit card on hold as it can literally separate the money from the care as a patient has automatic payments and hopefully paid off within just a few months.
- One thing to be careful about what credit card on hold is to not have a charged on the initial EOB unless the patient has already agreed to it. Sample of this would be a surgery where the patient knows their liability before the procedure.
- As we know sometimes insurance has denied an error and it is our job to work on behalf of the patient. Therefore we have to give enough time for the patient to become involved and appeal if necessary..

MEDICAL IDENTITY THEFT

It is estimated that one in three health records will be compromised or stolen

The impact of medical identity theft

- (Phi) is highly valuable on the black market
- It can be used to obtain pharmaceuticals, commit insurance fraud or obtain free medical care
- According to the FBI stolen health information currently fetches $60-$70 on the black market, while a social security number goes for $1.
- The costs are not just monetary. Medical identity theft can cause delays in treatment, misdiagnosis and inappropriate care, which can become life threatening.

Implement controlled access - make sure users are only granted access to information pertinent to their position.

- Ask your vendors what they have that may detect theft activity.

It really is about knowing the patterns of your practice so you can most likely track the source of those changes.

TO MAINTAIN AND MONITOR AN APPROPRIATE AND BALANCED INVENTORY

Story- an employee - stole baby formula samples – and then sold on ebay!

Story – dermatology office staff stealing and selling samples that the physician was unaware they had ever received!

•**Controlled substances?**

•Internal controls ensure that utilized by patients only

•Zero charge services posted? Be sure to have written doctor approval.

• The lack of knowledge of basic bookkeeping coupled
With the complexity of dealing with insurance and co-payments
Often discourages providers from becoming actively involved
In the accounting and bookkeeping tasks of the business.
•It is daunting!
•It's not surprising that doctors depend on managers.
• Doctors are most typically the manager's check and balance!
•Be involved on a daily basis
•Sign off on daily reports and look at what is being signed
•Meet with manager periodically
•Support our policies
Would recommend to have one doctor be financial partner with manager on annual or bi-annual basis.

- Look at the back up of every invoice including credit cards !
- Erasable ink anyone? Vendor matches who deposited check
- Vendor with exceptionally high activity
- Refunds issued
- Bank accounts---verify all accounts with banks

- Q: blank checks have been signed by doctors as they are hurrying out the door? (Never do it!)

- **Lesson learned**? • Copy/scan - or have duplicate deposit slips (compared to bank rec)

- Look at your actual deposit slip and compare the breakdown of types of payments to your system deposit slip.

TRUST AND VERIFY- ALWAYS CONFIRMING FINANCIAL TRANSACTIONS

•Keep a list of money handlers

•more than one person a day to sign off on each other

•**Income other than fee for service should have its own deposit**. Eg- medical records rental income

•**Depending upon each provider's contract** - depositions, for example may need to be given directly to the doctor.

•Your presence in daily reconciliations and deposits, monthly write-up, and so on…has a substantial impact and helps financially secure your practice

OUR LIVES ARE NOT STATIC - SUDDEN CATASTROPHE OR CRISIS CHANGE ONE'S LIFE IN A SECOND!
Reasons to embezzle?
•No ethical standards in place by anyone
•May simply be bored and looking for excitement
•No raises for a long time
•Employees do not like or respect either those in charge,
Here are some ways to do it!
•Employee takes cash payment from patient and does not post charge or payment.
• Employee gives patient a fictitious receipt for payment that was made.
• Employee gives busy doctor a sheaf of checks to sign, includes an extra one.
• Refund check made out to fictitious patient. (Employee opened an account under that name)
• rubber stamp is made of doctor's signature: uses to make extra paycheck for self.
Statements from those who have been caught as to why they did it:
•"It was just easy to take a little bit at a time."
•"Dr. Always took money from the petty cash and never paid it back. I guess i felt like the practice was just as much mine as his."
•"Dr. wastes more money than I ever took."
•"I figured Dr. gave so much care away, that he isn't going to miss a few dollars."
•"He never appreciated what i did, nor would he consider a raise without my begging—so I guess I just gave myself a raise.
•"Actually, I would have never been caught had I not taken a lunch hour."

How many perpetrator typically involved in the scheme?
•83% one person
•11% 2 people, and 5% more than 2
Behavior and signs
Some of these are more obvious than others
Here are a few….
• Employee does not take scheduled vacations, or takes only a day or two off.
•His or her lifestyle change and suddenly seems to be enjoying a greater lifestyle. These include:
• He or she abruptly changes spending patterns: new car, house, boat, clothes, or jewelry.
• Employee openly resents any overseeing of his or her work or new financial controls.
• The employee wants total control over all financial aspects or already keeps all office financial responsibilities for him or herself.
• Practice management system deposits do not balance with accounting ledgers
• Employee is overzealous about collecting and never seem to bring results.
• More overtime than usual is paid to staff and work is still not current.

PROTECT YOUR PRACTICE!

•Who outside of your office has access to your financial information?

•Electronic access to buildings and systems that can be changed in a nanno second.

•An internal framework to protect network security is a must!

•Please speak with your security people to be sure of your security on all levels

•Make sure that you have documented list of vendors and contacts within that company

•**Does anyone still have an in-house server?** If so please do verify that you're back ups are being conducted as you expect them to be – don't assume a thing.

BE AWARE OF YOUR EMPLOYEES AND THEIR PROBLEMS AND ANGSTS

Be vigilant for employees desperate enough to become thieves.

SCRUTINIZE RESUMES

• Check references, but don't use the phone numbers helpfully provided.

•Look them up yourself so you will know that you are really speaking with the reference and not a friend of the prospective employee

LOOK FOR INCONSISTENCIES — MAKE SURE EVERYTHING JIVES - Ask previous employers where the applicant worked before and compare the answer with what's on the resume

ASK FORMER EMPLOYERS TO CONFIRM EXACT DATES OF EMPLOYMENT — Applicants sometimes try to cover a checkered past by "stretching" the dates of favorable employment experiences.

Investigate your suspicions —pay attention do your instincts.

•Conduct a background check on all employees regardless of prior relationships with employees.

•This may include a detailed credit check on any employee who will have access to money**.**

•**It's important to note that many embezzlers have no criminal history.**

HIRE AND KEEP THE BEST ONES AND REDUCE YOUR CHANCES OF EMBEZZLEMENT!!
Think about it- the people who want a career do not necessarily want jail to be a part of their future

•True professionals usually want a clean record and will not steal!
•Reward longevity
•Respect their role and time – e.G. Be on time for staff meetings –
•If they feel good about their role and ties to the practice- they are less apt to do anything negative…..

•**PERSONNEL MANUAL — BE CLEAR AND CONCISE**
•Warn all employees of the consequences – if caught stealing or committing fraud= automatic dismissal
•Register crime with the authorities and legally prosecute – to the fullest degree
•Require restitution
•Every situation is different - be willing to forgive & forget

•**EXIT INTERVIEWS –** Look for opportunities to get information e.g. - we all want to be her his is a perfect opportunity to speak their mind because they're about to walk out the door ….

•**LOOSE LIPS SINK SHIPS –** If they feel they have never been listened to or angry, they will tell you everything !

IF YOU BELIEVE SOMEONE MAY BE EMBEZZLING?

•Call your attorney
•Call your liability carrier
•Meet with the docs
•When you discuss- have a witness in the room
•Be sure to record for personnel file
•Register crime with the authorities
•Legally prosecute – to the fullest degree
•It takes effort to convince a doctor that his office manager was a thief.
•My own personal experiences include ties when the physician said to me" but shes a good long time employee!"
•We want to believe that this would never happen –
•I've never heard anyone say gee, I thought they were stealing…
•As you return to the office, please check with your liability carrier and other professionals regarding risk management and fully safeguarding your practice

TRUST AND VERIFY! THAT IS ACCOUNTABLILITY! AND ANY GOOD EMPLOYEE WILL WELCOME THAT!

Throughout the financial management processes and procedures:

•It will strengthen loyalty
•As you build a bond with staff, this reduces chances of theft.
•That personal connection is a wonderful thing for all of us
•A nice bonus? The patients really notice that!
•It is most important to clearly define protocols that lead your practice successfully including essential financial checks and balances!

Resources

- CPA Professional Associations
- Medical Specialty Groups and Societies
- Medical Group Medical Managers Association (MGMA)
- Your Peers

SELF EVALUATION

Understanding and Safeguarding Against Practice Embezzlement

1. It is projected during a five (5) year period of time; over of all, what percentage medical practices will experience embezzlement in one form or another.

a. 50%
b. 65%
c. 80 %

2. If you are working with a billing company, one way to track ACH amounts deposited to the money amount applied, is to:

a. Match the daily bank deposits to payer reports and your practice management system.
b. Have the billing company send you a list of their applications weekly.
c. Reconcile deposits at month-end.

3. T/F - The CEO or Medical Director is most typically the one who signs the accounts payable and payroll checks. That is also the only person to approve new vendors.

4. It is recommended that the lead physician sign off on activity for charges and deposits:

a. Every two or three days
b. Weekly
c. Daily

5. Regarding payroll, how often should pay rates be reviewed for the accuracy of correct wages?

a. Quarterly
b. Monthly
c. Annually

6. T/F - Credit card on hold is a great process for checks and balances because the information is tokenized and kept offsite.

7. Which of the following is not a “sign” that an employee may be embezzling?

a. The employee does not take scheduled vacations, or takes only a day or two off.
b. The employee constantly works overtime, takes work home, and is seldom absent.
c. The employee goes out to lunch every day.

Answer Key: 1. C, 2. A, 3. T, 4. C, 5. B, 6. T, 7. C