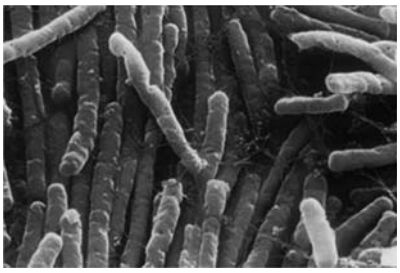
50th Annual Primary Care Review

Thursday

OHSU

The Current Pandemic and New Treatment Approaches to *Clostridioides difficile*.



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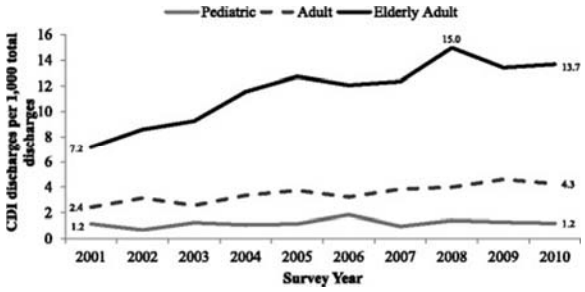
OSU Oregon State University OHSU College of Pharmacy

Side note: Nomenclature Changes

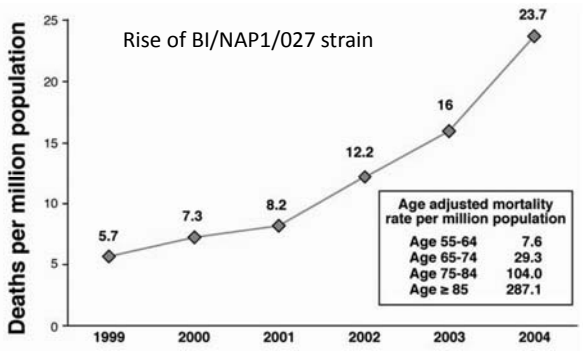
CLSI AST News Update. 2018; 3(1): 1-21.

Increasing Incidence



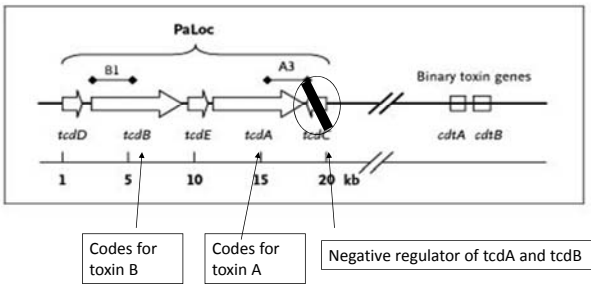
BMC Infect Dis. 2016; 16: 682.

Increasing Severity



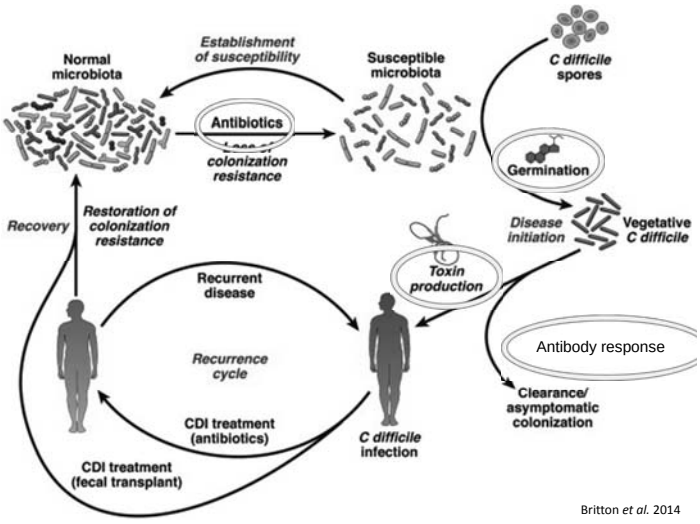
Gastroenterology 2009;136:913–1924

Toxins A and toxin B are produced in the Pathogenicity Locus (PaLoc) of *C. difficile*



tcdC deficient strain BI/NAP1/027 = Lots more production of toxins A and B!

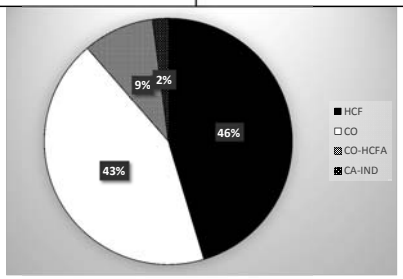
McDonald et al. N Eng J Med 2005;353:2433-2441



Britton *et al.* 2014

C. difficile not only a hospital disease

2.8 million hospital admissions	342 million outpatient visits



Clinical Infectious Diseases, ciy715, https://doi.org/10.1093/cid/ciy715

Community Risk Factors – age, abx, PPI

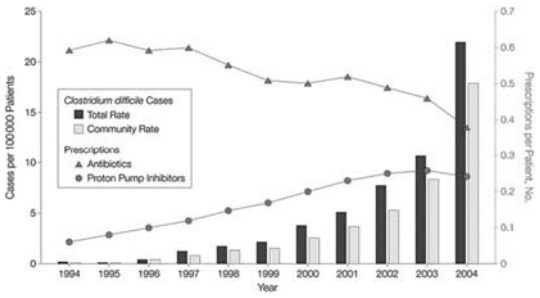
Table 2 Analysis of risk factors for community-associated *C. difficile* infection

Variable	CA-CDI Cases (N = 304)	Controls (N = 3040)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Age in Years (by category)				
<18 years	45 (14.80)	814 (26.78)	reference	reference
19 to 49 years	125 (41.12)	1296 (42.63)	0.94 (0.74, 1.19)	1.92 (1.32, 2.78)
50 to 64 years	106 (34.87)	803 (26.41)	1.49 (1.16, 1.91)	2.36 (1.59, 3.49)
65 to 74 years	18 (5.92)	92 (3.03)	2.03 (1.21, 3.43)	3.38 (1.73, 6.57)
≥75 years	10 (3.29)	35 (1.15)	2.90 (1.43, 5.90)	2.49 (1.01, 6.12)
Gender (female)	184 (60.53)	1570 (51.64)	1.44 (1.1, 1.83)	1.24 (0.95, 1.61)
History of Hospitalization in Previous Year	33 (10.86)	103 (3.39)	3.47 (2.30, 5.23)	1.60 (0.99, 2.60)
Charlson Comorbidity Index [Mean (SD)]	0.17 (0.62)	0.05 (0.27)	2.03 (1.55, 2.64)	1.33 (0.98, 1.79)
Inflammatory Bowel Disease	12 (3.95)	4 (0.13)	30.0 (9.68, 93.02)	41.89 (11.83, 148.35)
Antimicrobial Use				
None	82 (26.97)	2120 (69.74)	reference	reference
Any	222 (73.03)	920 (30.26)	6.12 (4.70, 7.98)	6.09 (4.59, 8.08)
Gastric Acid Suppressant Use†				
None	249 (81.91)	2883 (94.84)	reference	reference
Any	55 (18.09)	157 (5.16)	4.07 (2.91, 5.69)	2.30 (1.56, 3.39)

NOTE. Data are number (%) of patients, unless otherwise stated.
* Adjusted for all other covariates
† Includes proton pump inhibitors and histamine-2 receptor antagonists.

Kuntz et al. BMC Infectious Diseases 2011, 11:194

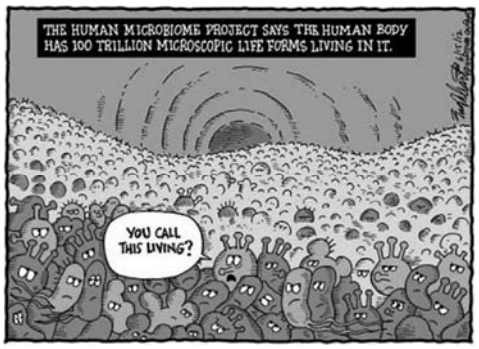
Rates of *Clostridium difficile* per 100 000 Patients in the United Kingdom General Practice Research Database



Dial: JAMA 2005;294(23):2989–95

To start: why do we get C diff in the first place?

Welcome to the wonderful world of the microbiome!



Gut microbiota: 16S RNA sequencing

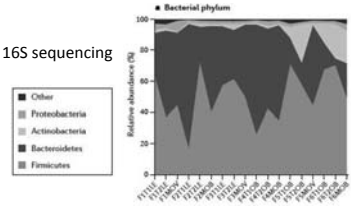
Firmicutes:
Mostly good (C diff is a firmicute)
Mostly spore formers (think: probiotic)
Usually largest component of microbiota

Bacteroidetes
Mostly good (Bacteroides predominates)
Non-spore forming
Usually tied for largest component

Actinobacteria
Mostly good
Not very common, sort of the ugly stepsister of the healthy microbiota

Proteobacteria
Good in small quantities (this is E. coli, Klebsiella, etc
This is where the 'overgrowth' occurs after antibiotic therapy

16S sequencing

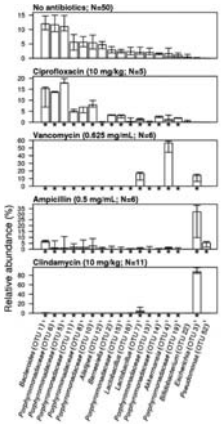


Adult asx C.diff carriage : 7-15%

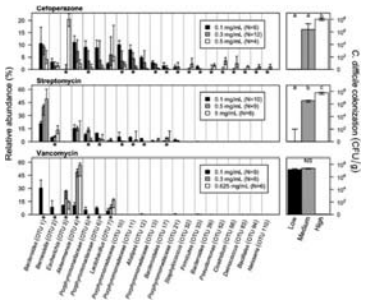
Cho et al. Nat Rev Genet 2012;13:260-70
J Clin Microbiol. 2014 Jul;52(7):2406-9

Mice exposed to a variety of antibiotics for 5 days

5 days of antibiotics are more than enough to completely change the microbiota

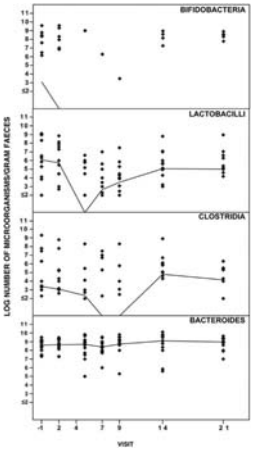


....and this disruption is more than enough to support C diff colonization



Schubert et al. mBIO 2015;6:e00974

The effect on the microbiome starts almost immediately



- 14 healthy volunteers given ceftaroline-avibactam X 7 days
- Changes in microbiota assessed over 21 days

Rashid et al. AAC 2015;59:4504-9

We are now able to predict the antibiotics most likely to cause CDI!!

- Any antibiotic that kills firmicutes and/or bacteroides will almost immediately increase CDI risk
- Thus: the most common antibiotic used with these properties will be the most likely to be associated with CDI

Antibiotics that increase CDI risk

Drug	Kills firmicutes	Kills bacteroidetes	Commonly used
Ampicillin-sulbactam	Yes	Yes	Medium
Cefepime	Yes	No	Yes
Ceftriaxone	Yes	No	Yes
Carbapenems	Yes	Yes	Yes and increasing
Piperacillin-tazobactam	Yes	Yes	Yes
Clindamycin	Yes	Yes	No
Flouroquinolones	Yes	Yes	Not as much

Which antibiotics are risk factors?

30-day risk of CDI among 97,130 hospitalized patients of whom 1,481 developed CDI

Individual Antibiotic	OR (ABX Received (Y/N))	*P*-Value	Antibiotic Use
Ampicillin/Sulbactam	1.640	0.012	1.7%
Cefepime	1.673	< 0.001	16.1%
Ceftriaxone	1.464	< 0.001	21.8%
Ertapenem	1.864	< 0.001	3.6%
Imipenem	2.077	< 0.001	3.2%
Meropenem	1.335	0.020	2.8%
Piperacillin/Tazobactam	1.655	< 0.001	16.6%
Age	1.009	< 0.001	N/A
Proton Pump Inhibitor (Y/N)	1.375	< 0.001	N/A
Charlson Comorbidity Index	1.208	< 0.001	N/A

OR – odds ratio; ABX - antibiotic

Davis M et al. Clin Microbiol Infect. 2018 Nov;24(11):1190-1194.

Despite our best efforts, C diff infection will be hard to prevent!

71 year old female with congestive heart failure, GERD, diabetes, and a past history of breast cancer.

Recently discharged after a 2-week hospitalization for bacterial pneumonia

She now presents to her PCP with watery diarrhea, leukocytosis (11,000 cells/mL) and elevated serum creatinine (1.1 mg/dL).

Stool is sent to the clinical microbiology and the stool tests positive for *C. difficile* toxins.

Betty B

How do you want to treat Betty B?

1. Metronidazole 500 mg PO three times daily
2. Vancomycin 125 mg PO four times daily
3. Vancomycin 250 mg PO four times daily
4. Fidaxomicin 200 mg PO twice daily
5. Vancomycin + metronidazole

*Treat for 10 days (usually)

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[3,4] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[1] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

There has been an explosion in treatment possibilities for CDI

Current: Probiotics
FMT
Use narrow-spectrum antibiotics

Metronidazole
Vancomycin
Fidaxomicin

IVIG
Monoclonal antibodies vs. C diff toxins

Future: 2nd generation FMT
non-tox C diff M3
Ecobiotics

Ridinilazole

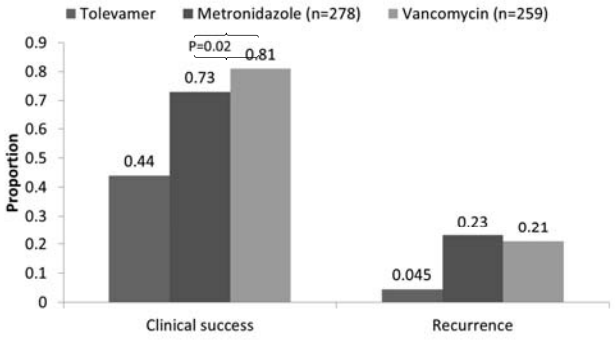
Toxoid vaccines

US IDSA CDI guidelines 2010

Episode	Clinical Signs	Severity	Recommended agent	Dosing Regimen	Strength of Recommendation
Initial	WBC < 15,000 and SrCr < 1.5 X premorbid level	Mild or moderate	Metronidazole	500 mg PO three times daily 10-14 days	A-I
Initial	WBC ≥ 15, 000 or SrCr ≥ 1.5 X premorbid level	Severe	Vancomycin	125 mg PO four times daily 10-14 days	B-I
Initial	Hypotension, shock, ileus, megacolon	Severe, complicated	Vancomycin + metronidazole IV	Vancomycin: 500 mg PO or NG four times daily + Metronidazole: 500 mg IV q8hours. For ileus, consider adding rectal instillation of vancomycin	C-III
Second (1st recurrence)	----------	----------	Same as initial	Same as initial	A-II
Third (2nd recurrence)	----------	----------	Vancomycin	PO tapered and/or pulsed	B-III

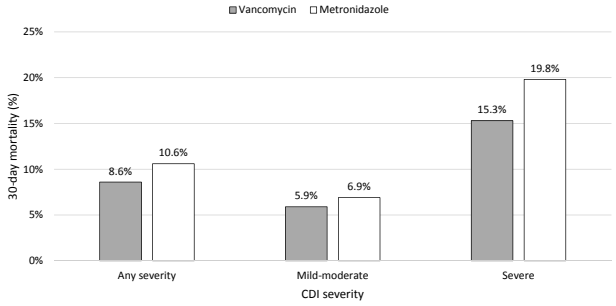
Cohen SH, Gerding DN, et al. Infection control and hospital epidemiology. 2010 (May); 31(5)

More recently, metronidazole has been shown to be globally inferior to vancomcyin (tolevamer phase III RCT)



Johnson S et al. Clin Infect Dis. 2014;59:345-354

Increased failure rate of metronidazole also associated with increased 30-day mortality



VA dataset (vancomycin: n=2,068; metronidazole: n=8,069 propensity matched). Patients given vancomycin had a significantly lower risk of 30-day mortality (RR: 0.86, 95% CI: 0.74-0.98). No difference in CDI recurrence regardless of disease severity or choice of antibiotic (16.3-22.8%)

Stevens et al. JAMA Int Med 2017

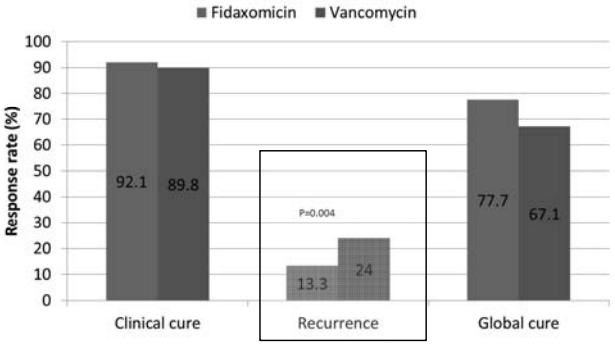
Summary of metro vs. vanco clinical studies

									Clinical failure		Recurrence	
Study	Year	Location	n	Single center	Blinded	Randomized	Metro dose	Vanco dose	metro	vanco	metro	vanco
Teasley, 1983	82-83	MN	101	yes	no	yes	250 mg QID	500 mg qid	2 of 37 (5.4%)	0 of 45 (0%)	2 of 37 (5.4%)	6 of 45 (13%)
Wenisch, 1996	93-95	Austria	62	yes	no	yes	500 mg TID	500 mg tid	2 of 31 (6%)	2 of 31 (6%)	5 of 31 (16%)	5 of 31 (16%)
Musher, 2006	02-04	USA (Houston)	34	no	yes	yes	250 mg QID	125 mg qid	6 of 34 (17%)	N/A	9 of 28 (32%)	N/A
Zar, 2007	94-02	Chicago	150	Yes	yes	yes	250 mg QID	125 mg qid	13 of 79 (16%)	2 of 71 (3%)	9 of 66 (14%)	5 of 69 (7%)
Johnson, 2013	05-07	World	552	no	yes	yes	375 mg QID	125 mg qid	76 of 278 (27%)	49 of 259 (19%)	48 of 202 (23%)	43 of 210 (21%)

Recurrence is the rule!

Enter the fidaxomicin debate!

Fidaxomicin: Equal efficacy at vancomycin to cure patients and lessens the risk of recurrence



The second phase III study showed similar results (Crook et al. Lancet ID)

Louie et al. N Eng J Med 2011;364:422-310

Comparative Treatment Efficacy in CDI

Outcomes	No. of Participants	Resolution, %	*P* Value	Quality of Evidence
Direct comparisons of metronidazole and vancomycin				
Resolution at end (10 days) of treatment	843 (5 studies)	**87 (VAN)** 78 (MTR)	0.0008	High
Resolution of diarrhea at end of treatment without recurrence*	843 (5 studies)	**73 (VAN)** 63 (MTR)	0.003	High
Direct comparisons of fidaxomicin and vancomycin				
Resolution at end (10 days) of treatment	1105 (2 studies)	88 (FDX) 86 (VAN)	0.36	High
Resolution of diarrhea at end of treatment without recurrence*	1105 (2 studies)	**71 (FDX)** 57 (VAN)	<0.0001	High

*1 month after treatment; **56 days after treatment
VAN = vancomycin, MTR = metronidazole, FDX = fidaxomicin

McDonald LC et al. Clin Infect Dis 2018:66(7):987-94

Recommendation for initial treatment of CDI in adults

Clinical definition	Supportive clinical data	Recommended treatment
Initial episode, non-severe	WBC < 15,000 cells/mL and serum creatinine < 1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days Alternate if above agents are not available: metronidazole 500 mg three times daily by mouth for 10 days
Initial episode, severe	WBC ≥ 15,000 cells/mL or a serum creatinine > 1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	VAN 500 mg given four times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of VAN. Add intravenous metronidazole 500 mg every 8 hrs if ileus present

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

- McDonald LC et al. Clin Infect Dis 2018:1-48

Explosion in treatment possibilities for CDI minus 1

Current: Probiotics
FMT
Use narrow-spectrum antibiotics

Vancomycin
Fidaxomicin

IVIG
Monoclonal antibodies vs. C diff toxins

Future: 2nd generation FMT
non-tox C diff M3
Ecobiotics

Ridinilazole

Toxoid vaccines

Recommendation for recurrence of CDI in adults

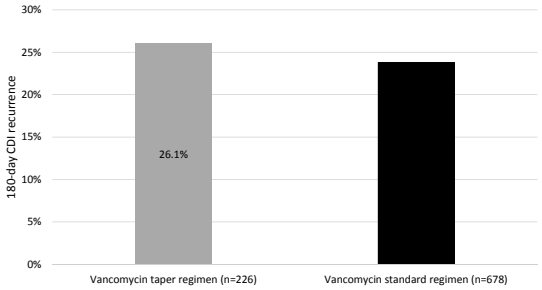
Clinical definition	Supportive clinical data	Recommended treatment
First recurrence		• VAN SD if metronidazole was used for the first episode OR • Prolonged tapered and pulsed VAN if VAN SD was used for first regimen OR • FDX SD if VAN was used for the initial episode
Second or subsequent recurrences		• VAN in a tapered or pulsed regimen OR • VAN SD followed by rifaximin 400 mg three times daily for 20 days OR • FDX SD OR • Fecal microbiota transplantation

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

McDonald LC et al. Clin Infect Dis 2018;xx(00):1-48

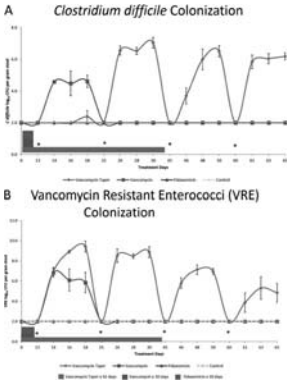
There is not a whole lot of data to support pulse taper oral vancomycin for recurrence prevention

Propensity matched analysis between standard and tapered oral vancomycin for adult patients treated for recurrent CDI, VHA dataset



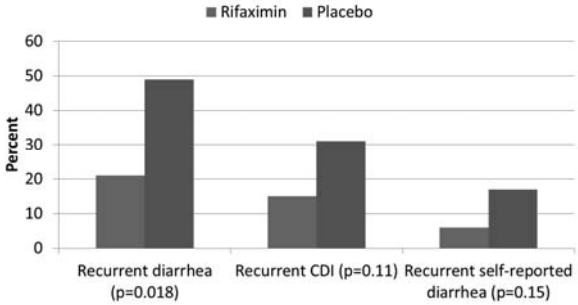
Gentry et al. Open Forum Infect Dis 2017;4(4):ofx235

Vancomycin extended taper regimen continues to disrupt the microbiome and allows for overgrowth of Clostridium difficile (A) and vancomycin-resistant enterococci (VRE) (B).



Myreen E. Tomas et al. Antimicrob. Agents Chemother. 2018;62:e02237-17

A randomized double-blind placebo-controlled pilot study to assess the effect of rifaximin to prevent recurrent diarrhea in 68 patients with *Clostridium difficile* infection



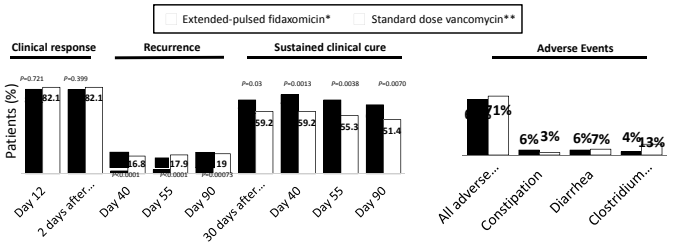
Patients were given a 20-day course of rifaximin or matching placebo after completing a 10-14 days course of metronidazole or vancomycin therapy

33

Garey et al. J Antimicrob Chemother 2011;66:2850-5

Extended-Pulsed Fidaxomicin vs. Standard Dose Vancomycin in Patients >60 years of age

EXTEND: randomized, controlled, open-label, phase 3b/4 trial in 181 patients ≥60-year-old with initial or recurrent CDI confirmed by presence of toxins A or B in stool sample

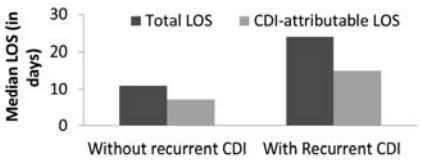


*Fidaxomicin: 200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25
**Vancomycin: 125 mg oral capsules, four times daily on days 1–10
Guery B, et al. *Lancet Infect Dis.* 2017;18(3):296-307.

Drug Costs

Medication	Formulation	Institutional Cost
~~metronidazole 500mg po q8h~~	~~tablet~~	~~$2.19/day~~
vancomycin 125mg po QID	capsule	$127.32/day
vancomycin 125mg po QID	oral solution	$20.00/day
vancomycin 250mg po QID	capsule	$188.63/day
vancomycin 250mg po QID	oral solution	$21.00/day
Fidaxomicin 200 mg PO BID	Tablet	$280/day

Increased healthcare utilization = increased healthcare costs



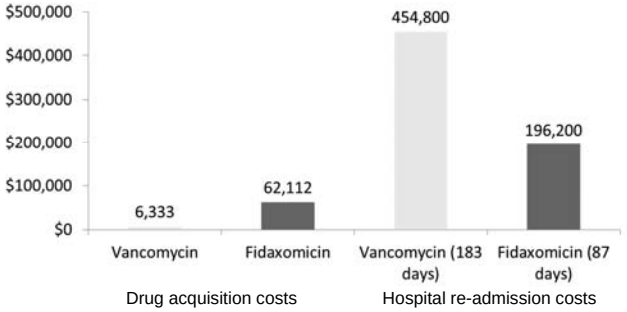
Cost in US dollars; median (IQR)	Without recurrent CDI	With recurrent CDI
CDI pharmacologic treatment*	$60 (23 - 200)	$140 (30 - 260)
CDI-attributable hospitalization^	$13, 168 (7,525 - 24,455)	$28, 218 (15, 049 – 47,030)
Total hospitalization^	$20, 693 (11, 287 - 41, 386)	$45, 148 (20, 693 - 82,772)

Shah et al. J Hosp Infect 2016 Jul;93(3):286-9

Any evidence that fidaxomicin may reduce these costs?

Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients.

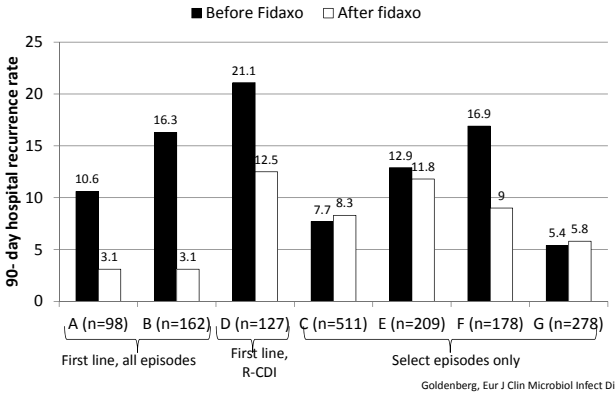
CDI-related re-admissions: Fidaxo: 20.4%; Vanco: 41.3%



Gallagher et al. AAC 2015

Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13 : seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)



Goldenberg, Eur J Clin Microbiol Infect Dis 2016

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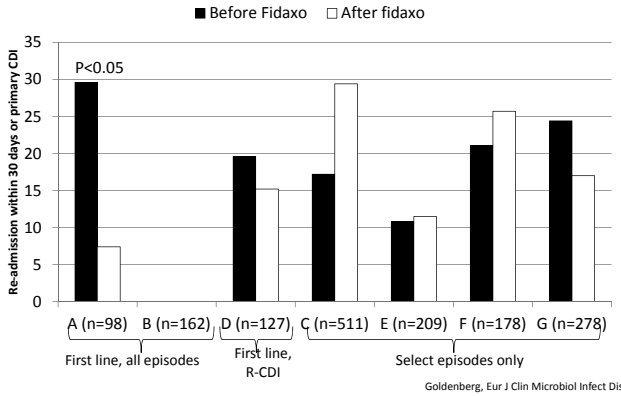


Goldenberg, Eur J Clin Microbiol Infect Dis 2016

Why fidaxomicin should be used first-line…

Question	Answer	Why
Is fidaxomicin a superior drug?	Yes	Decreased recurrence rate by 50%
Is fidaxomicin a safer drug?	Yes	Decreased VRE colonization
Is fidaxomin a more cost-effective drug?	Yes	Decreased hospitalization costs due to recurrent C diff
Is patient satisfaction higher if you don't have recurrence?	Yes	Significantly increased anxiety in patients with recurrent C diff

Why vanco should be used first line…

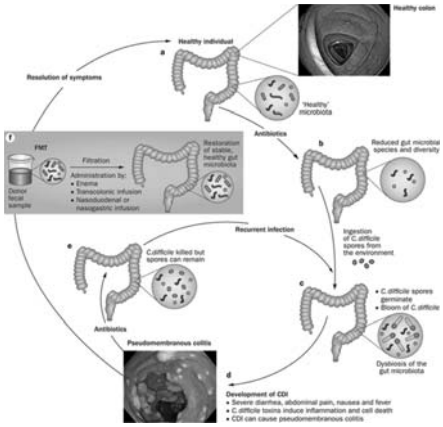
- Remarkably effective at initial clinical cure
- Decades of experience, has withstood the tests of time
- With a little creativity, (dose taper, probiotics?) can lower recurrence rates similar to what is observed with fidaxomicin

Vancomycin is remarkable effective at day 7-10 cure rates

Study years	Study drug	Comparator	Study phase	N	Clinical cure		Recurrence rate	
					Study drug	Vanco	Study drug	Vanco
<2005	Ramoplanin	Vancomycin	II	89	71	78		
2006-08	Fidaxomicin	Vancomycin	III	629	88	90	15	25
2007-09	Fidaxomicin	Vancomycin	III	535	88	87	13	27
2010-11	Surotomycin	Vancomycin	II	209	87-92	89	17-28	36
2012-15	Surotomycin	Vancomycin	III	608	79	84	18	23
2012-15	Surotomycin	Vancomycin	III	608	83	82		
2011-12	Cadazolid	Vancomycin	II	84	68-80	68	18-25	50
2011-12	LFF571	Vancomycin	II	72	85	80	31	30
2014-15	Ridinilazole	Vancomycin	II	100	78	70	14	35

Basseres et al. Curr Opin Gastronenterol 2017;33:1-7

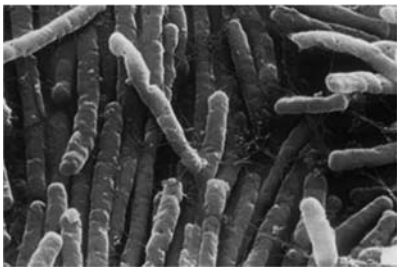
Fecal Microbiota Transplant (FMT)



Final Thoughts

- CDI increasing, maybe new norms
- Gut microbiota better understaning
- New guidelines
  - Metronidazole out
  - Vancomycin vs fidaxomicin battles
- Recurrence still problematic
  - FMT
- Future areas – abx, gut protection, host response

The Current Pandemic and New Treatment Approaches to *Clostridioides difficile*.



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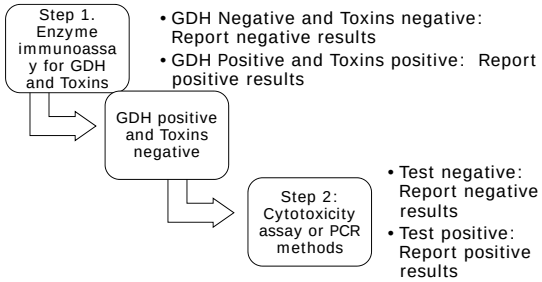
Effective use of Evolving diagnostic tests for CDI detection



How Well do Drugs Work?

Craig Williams, PharmD., BCPS, FNLA
Clinical Professor, OSU/OHSU College of Pharmacy
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Conflicts of interest: None

Perspective
FEBRUARY 22, 2018

The Psychology of Clinical Decision Making — Implications for Medication Use

Jerry Avorn, M.D.

NEJM, February 22nd 2018

1. Newer anticoagulant drugs do not require monitoring and produce different outcomes when used for different clinical indications. In which of the following circumstances would you be most likely to recommend a newer anticoagulant?

   a. If it was found to provide a relative reduction in total mortality of 20%
   (b.) If it increased the likelihood of survival from 95% to 97%

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   a. A 10% absolute risk reduction in moderate and severe COPD exacerbations per year
   (b.) A 15% relative risk reduction in moderate and severe COPD exacerbations per year

"Medications do not work in patients who do not take them."

C. Everett Koop, MD
Former Surgeon General of the United States

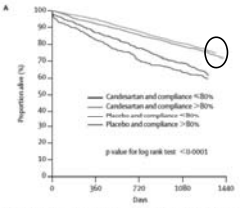
only
"Medications ~~do not~~ work in patients who do ~~not~~ take them."

C. Everett Koop, MD
Former Surgeon General of the United States

Even placebos work better in those who take them….

Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial

Brad B Granger, Karl Swedberg, Inger Ekman, Christopher B Granger, Bertil Olofsson, John J V McMurray, Salim Yusuf, Eric L Michelson, Marc A Pfeffer, for the CHARM investigators



Good adherence to placebo reduced mortality compared to poor adherence to ARB

Adherence to the ARB was barely better than adherence to placebo

Interpretation Good adherence to medication is associated with a lower risk of death than poor adherence in patients with CHF, irrespective of assigned treatment. This finding suggests that adherence is a marker for adherence to

Many drugs with small yet statistically significant benefits form the backbone of national guidelines. How effective are these drugs?

ACEI and ARB therapy for kidney protection

A patient who had been on ACE-I therapy presents to clinic one week after being treated in the E.D. for a potassium concentration of 6.3 mEq/L with ECG changes. The ACE-I has been held for past week and in clinic, the blood pressure is at goal (on a CCB) and you must now decide whether to re-start ACE-I therapy for nephroprotection.

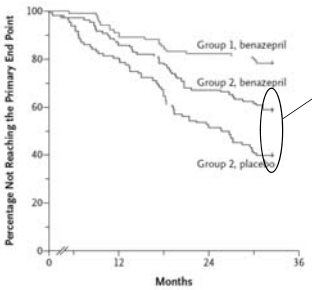
In which of the following patients are you more likely to recommend resumption of ACE-I (if equal in both, OK to indicate both)?

a. A 42 year old with T1DM and an A1C of 8.5% but no nephropathy
b. A 42 year old without DM and a S_{cr} of 3.5 mg/dL

The clinical benefit in b. is infinitely greater than the benefit in a.

Drugs are generally very inefficient at preventing disease as compared to treating disease

ACE-I/ARB therapy treats nephropathy. The worse any disease, the lower the NNT to avoid a bad outcome. ACE-I for progression to ESRD:



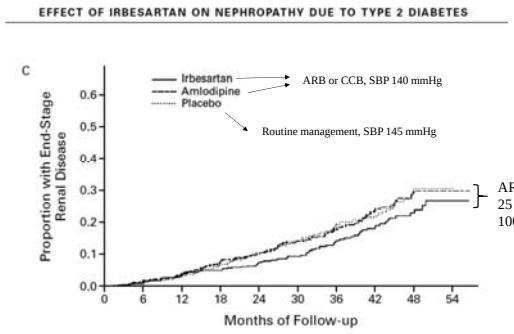
Group 1: baseline S_{cr} 1.5-3.0 mg/dL
Group 2: S_{cr} 3.0-5.0 mg/dL

ARR about 20% at 3-yrs for NNT ~ 5

Primary End Point: ESRD or death (but there was only 1 death in the trial)

NEJM 2006;354:131-40

IDNT trial: NEJM Sept, 2001: High risk patients with diabetic, hypertensive CKD and baseline S_{cr} 1.7 mg/dL



ARR~ 4%, NNT ~ 25 over 4 years or 100 patients per year

From the standpoint of magnitude: Less disease = Less benefit from pharmacotherapy and a greater NNT to avoid a clinically important outcome.

For ACE-I/ARB therapy for nephroprotection (avoiding ESRD):

1. NNT = 5 over 3 years with S_{cr} 3.5 mg/dL
2. NNT = 25 over 4 years with S_{cr} 1.7 mg/dL (1/6 the benefit)

A patient who had been on ACE-I therapy presents to clinic one week after being treated in the E.D. for a potassium concentration of 6.3 mEq/L with ECG changes. The ACE-I has been held for past week and in clinic, the blood pressure is at goal (on a CCB) and you must now decide whether to re-start ACE-I therapy for nephroprotection.

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ORIGINAL ARTICLE

N Engl J Med 2009;361:40-51

Renal and Retinal Effects of Enalapril and Losartan in Type 1 Diabetes

Michael Mauer, M.D., Bernard Zinman, M.D., Robert Gardiner, M.D., Samy Suissa, Ph.D., Alan Sinaiko, M.D., Trudy Strand, R.N., Keith Drummond, M.D., Sandra Donnelly, M.D., Paul Goodyer, M.D., Marie Claire Gubler, M.D., and Ronald Klein, M.D., M.P.H.

Over 5 years of follow-up, there were no cases of elevated Scr and no benefit in terms of onset of proteinuria (trend went the wrong direction for losartan)

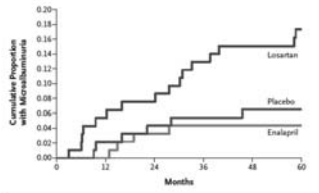

Figure 2. Kaplan–Meier Estimates of Time to Microalbuminuria.

A patient who had been on ACE-I therapy presents to the Family Medicine clinic one week after being treated in the E.D. for a potassium concentration of 6.3 mEq/L with peaked t waves. In clinic, the blood pressure is at goal on a CCB and you must now decide whether to re-start ACE-I therapy.

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a. A 42 year old with T1DM and an A1C of 8.5% but no nephropathy
b. A 42 year old without DM and a S_{cr} of 3.5 mg/dL

In any discussion of risks vs. benefits of resuming ACE-I in these patients, a case cannot be made for a. whereas a fairly compelling case still exists for b.

1. Newer anticoagulant drugs do not require monitoring and produce different outcomes when used for different clinical indications. In which of the following circumstances would you be most likely to recommend a newer anticoagulant?

   a. If it was found to provide a relative reduction in total mortality of 20%
   (b) If it increased the likelihood of survival from 95% to 97%

2. New GOLD guidelines for COPD have reduced the role of inhaled steroids in favor of dual, long-acting bronchodilator therapy. Compared to single long-acting bronchodilator therapy, which of the following findings would make you more likely to prescribe dual bronchodilator therapy?

   a. A 10% absolute risk reduction in moderate and severe COPD exacerbations per year
   b. A 15% relative risk reduction in moderate and severe COPD exacerbations per year

Anticoagulation and Clinical Outcomes……..The DOACs

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2017 VOL. 377 NO. 14

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn,

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66–0.86)	<0.001	0.90 (0.79–1.03)	0.12
Secondary outcomes‡							
Ischemic stroke, myocardial infarction, ALI, or death from CHD	329 (3.6)	397 (4.4)	450 (4.9)	0.72 (0.63–0.83)	<0.001	0.88 (0.77–1.01)	0.06
Ischemic stroke, myocardial infarction, ALI, or CV death	389 (4.3)	453 (5.0)	516 (5.7)	0.74 (0.65–0.85)	<0.001	0.88 (0.77–0.99)	0.04
Death from any cause	313 (3.4)	366 (4.0)	378 (4.1)	0.82 (0.71–0.96)	0.01	0.97 (0.84–1.12)	0.67

Rivaroxaban increased the likelihood of survival from 95.9% to 96.6%

18% RRR

But maybe "death" by itself is not a fair outcome for DOACs since they also reduce MI and stroke in patients with CVD.
While that is a good point, remember that DOACs also have serious side effects

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice

So maybe fair to come up with a composite outcome that takes into account major benefits beyond just survival but also accounts for the risks of serious bleeding….

If we take into account CVD events along with death and factor in fatal and major clinical bleeding:

Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)

The RRR is now exactly 20%

Likelihood of remaining event free increases from 94.1% to 95.3%

1. Newer anticoagulant drugs do not require monitoring and produce different outcomes when used for different clinical indications. In which of the following circumstances would you be most likely to prescribe a newer anticoagulant?

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   b. If it increased the likelihood of survival from 95% to 97%

This is a bigger benefit. A reduction in mortality from 5% to 3% is a 40% RRR: 2/5=40%

Perspective
FEBRUARY 22, 2018

The Psychology of Clinical Decision Making — Implications for Medication Use

Jerry Avorn, M.D.

NEJM, February 22nd 2018

"We are moved by the prospect of harms or losses more than by identically sized benefits or gains."

Aside from just math (20% relative effect seems a lot bigger than a 1% absolute effect), avoiding death is a more compelling choice than gaining probability of living

SPECIAL ARTICLES

ON THE ELICITATION OF PREFERENCES FOR ALTERNATIVE THERAPIES

BARBARA J. MCNEIL, M.D., PH.D., STEPHEN G. PAUKER, M.D., HAROLD C. SOX, JR., M.D., AND AMOS TVERSKY, PH.D.

Abstract We investigated how variations in the way information is presented to patients influence their choices between alternative therapies. Data were presented summarizing the results of surgery and radiation therapy for lung cancer to 238 ambulatory patients with different chronic medical conditions and to 491 graduate students and 424 physicians. We asked the subjects to imagine that they had lung cancer and to choose between the two therapies on the basis of both cumulative probabilities and life-expectancy data. Different groups of respondents received input data that differed only in whether or not the treatments were identified and whether the outcomes were framed in terms of the probability of living or the probability of dying.

In all three populations, the attractiveness of surgery, relative to radiation therapy, was substantially greater when the treatments were identified rather than unidentified, when the information consisted of life expectancy rather than cumulative probability, and when the problem was framed in terms of the probability of living rather than in terms of the probability of dying.

We suggest that an awareness of these effects among physicians and patients could help reduce bias and improve the quality of medical decision making. (N Engl J Med. 1982; 306:1259-62.)

NEJM 1982;306:1259-62

The anticoagulant data from the patient perspective:

Imagine if a patient had been asked to take a drug because it reduced the odds of a major clinical event by 20%.

But then they read on a health blog that the benefit of a years worth of therapy was that their likelihood of not having a major clinical event rose from about 95% to about 96%.

Any of us might feel a little mislead….

2. New GOLD guidelines for COPD have reduced the role of inhaled steroids in favor of dual, long-acting bronchodilator therapy. Compared to single long-acting bronchodilator therapy, which of the following findings would make you more likely to recommend dual bronchodilator therapy?

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Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study

Jadwiga A Wedzicha, Marc Decramer, Joachim H Ficker, Dennis E Niewoehner, Thomas Sandström, Angel Fowler Taylor, Peter D'Andrea, Christie Arrasate, Hungta Chen, Donald Banerji

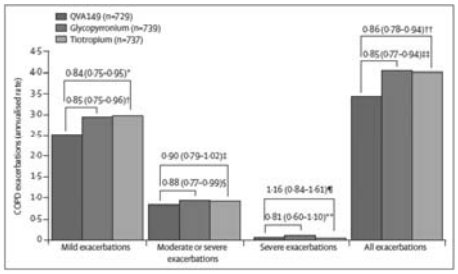
Lancet, May 2013: Dual bronchodilator vs. monotherapy

COPD exacerbations in clinical trials are a different beast compared to things like stroke and death in CVD trials. From SPARK trial:

Findings Between April 27, 2010, and July 11, 2012, 741 patients were randomly assigned to receive QVA149, 741 to receive glycopyrronium, and 742 to receive tiotropium (729, 739, and 737 patients, respectively, analysed for efficacy). QVA149 significantly reduced the rate of moderate to severe exacerbations versus glycopyrronium by 12% (annualised rate of exacerbations 0·84 [95% CI 0·75–0·94] vs 0·95 [0·85–1·06]; rate ratio 0·88, 95% CI 0·77–0·99, p=0·038). Adverse events (including exacerbations) were reported for 678 (93%) of 729 patients on QVA149, 694 (94%) of 740 on glycopyrronium, and 686 (93%) of 737 on tiotropium. Incidence of serious adverse events was similar between groups (167 [23%] patients

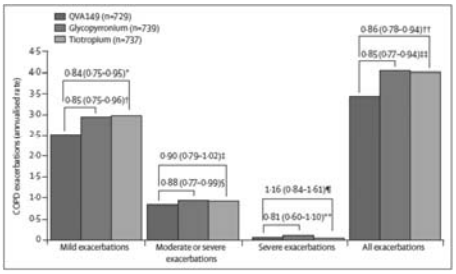
Rather than ~ 95% of patients NOT having primary events, we now have ~ 95% HAVING primary events…

This makes sense. Our sick COPD patients have a lot of exacerbations. But what are we talking about – need for an antibiotic, hospitalization??



SPARK trial, May 2013

Mild exacerbation…….. managed at home, usually with a little more acute reliever (i.e. albuterol)
Moderate…… requiring antibiotic or steroid (so accessing and utilizing health care resources)
Severe…… resulting in hospitalization



SPARK trial, May 2013

And the y-axis here is rate per patient per year

For moderate and severe exacerbations: About one per patient per year. What does that mean for our numbers and absolute vs. relative risk?

	Total number of exacerbations	Mean number of exacerbations per patient	Annualised rate (95% CI)*
Mild exacerbations (6969 events)			
QVA149 (n=729)	2105	2·89 (3·50)	2·51 (2·25–2·80)
Glycopyrronium (n=739)	2422	3·28 (3·89)	2·96 (2·66–3·29)
Tiotropium (n=737)	2442	3·31 (3·97)	2·98 (2·68–3·32)
Moderate or severe exacerbations (2610 events)			
QVA149 (n=729)	812	1·11 (1·35)	0·84 (0·75–0·94)
Glycopyrronium (n=739)	900	1·22 (1·48)	0·95 (0·85–1·06)
Tiotropium (n=737)	898	1·22 (1·66)	0·93 (0·83–1·04)
Severe exacerbations (364 events)			
QVA149 (n=729)	121	0·17 (0·47)	0·09 (0·07–0·13)
Glycopyrronium (n=739)	138	0·19 (0·49)	0·12 (0·09–0·16)
Tiotropium (n=737)	105	0·14 (0·47)	0·08 (0·06–0·11)
All exacerbations† (9488 events)			
QVA149 (n=729)	2893	3·97 (3·88)	3·44 (3·15–3·75)
Glycopyrronium (n=739)	3294	4·46 (4·39)	4·04 (3·71–4·40)
Tiotropium (n=737)	3301	4·48 (4·51)	4·02 (3·69–4·38)

When more events are happening (migraine prevention trials, epilepsy, COPD exacerbations) then relative and absolute risk reductions are mathematically similar….

2. New GOLD guidelines for COPD have reduced the role of inhaled steroids in favor of dual, long-acting bronchodilator therapy. Compared to single long-acting bronchodilator therapy, which of the following findings would make you more likely to prescribe dual bronchodilator therapy?

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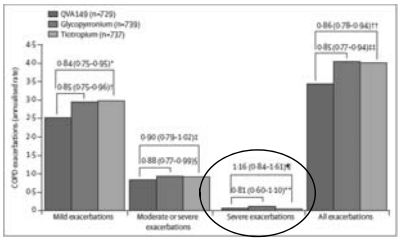
These are exacerbation rates per patient per year

By the numbers, for every 100 patients treated per year: 84 had a moderate or severe exacerbation on LABA+LAMA vs. 94 on monotherapy (LAMA) alone…..

ARR is 10% (94%-84%) and RRR in this case: 94-84/93 x 100 = 11%. So, any RRR > 11% is a larger benefit than a 10% ARR

But let's forget the math: how clinically effective is LABA+LAMA vs. monotherapy?

To avoid a hospitalization?



A: cost is infinity

How effective is it to use LAMA + LABA to avoid a moderate exacerbation?

How effective is it to use LAMA + LABA to avoid a moderate exacerbation?

Moderate or severe exacerbations (2610 events)			
QVA149 (n=729)	812	1·11 (1·35)	0·84 (0·75–0·94)
Glycopyrronium (n=739)	900	1·22 (1·48)	0·95 (0·85–1·06)
Tiotropium (n=737)	898	1·22 (1·66)	0·93 (0·83–1·04)

Remember, the absolute risk reduction with dual bronchodilator therapy vs. LAMA monotherapy is 10% (from 94 exacerbations per 100 patients treated to 84 exacerbations per 100 patients treated)

So…

$400 x 12 months of therapy x 10 patients needed to treat = $48,000 to avoid one exacerbation requiring a steroid or antibiotic

That's crazy right?

"Mrs. Jones, I'm going to charge you $48,000 for additional inhaled therapy to avoid the need to use an antibiotic or oral steroid burst for a moderate COPD exacerbation."

And yet….knowing this is unlikely to change our decision the next time we face a COPD patient with ongoing symptoms of COPD on a single long-acting bronchodilator

Perspective

FEBRUARY 22, 2018

The Psychology of Clinical Decision Making — Implications for Medication Use

Jerry Avorn, M.D.

"The bias of the individual patient…."

NEJM; April 19, 1990

OCCASIONAL NOTES

DISCREPANCY BETWEEN MEDICAL DECISIONS FOR INDIVIDUAL PATIENTS AND FOR GROUPS

Stanford University
Stanford, CA 94305

DONALD A. REDELMEIER, M.D.
AMOS TVERSKY, PH.D.

Our results are consistent with the notion that physicians give more weight to the personal concerns of patients when considering them as individuals and more weight to general criteria of effectiveness when considering them as a group. For example, the re-

So, resource utilization for the health of our individual patient does not always align well with the health of the health care system and Big PHARMA is pretty good at exploiting that so it is good to be aware of our biases

Summary:

1. Drugs are developed to treat disease and are often very inefficient at preventing disease (higher NNT)
2. Expensive drugs used in inefficient settings (dual bronchodilator) add significant cost burden to the health system
3. Being aware of our human biases may help us use drugs better

Thank you

Young adults with intellectual and physical disabilities and complex multi-system conditions

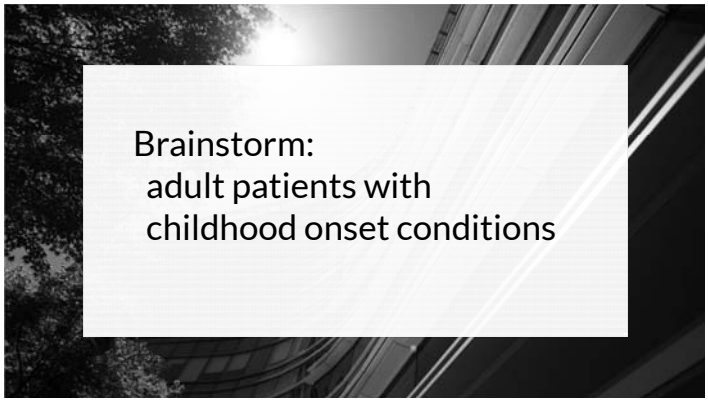
Special considerations and approach

Reem Hasan, MD PhD
Assistant Professor of Pediatrics and Internal Medicine, OHSU
Feb 14, 2019

Disclosures

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.
  - None to be discussed
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

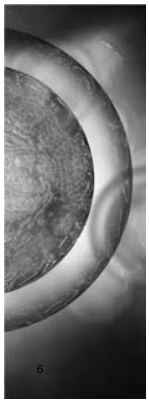
Introductions



Brainstorm: adult patients with childhood onset conditions

Objectives

- Describe specific steps that a primary care provider can take to overcome the barriers faced by adults with intellectual and physical disabilities and chronic diseases of childhood in seeking medical treatment in an adult care setting
- Create a plan that will implement at least one change in practice to accommodate patients with intellectual and physical disabilities and chronic diseases of childhood



Disparity in care

- Less care and support
- More gaps – transition is not smooth, streamlined
- Complexity, multiple systems
- Medical systems and community organizations
- Communication challenges
- Supporters/caregivers
- Need for coordination

Diversity of patients

- Healthy, typically developing patient
- Patient with chronic childhood-onset health condition but no impact on cognition
- Patient with significant cognitive impact precluding ability to care for self or make independent decisions

Example 1
Typically developing young adult

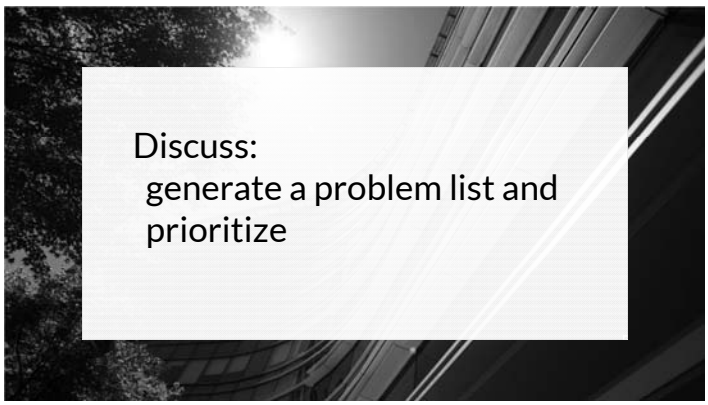
- Tina is a 22 year old woman who just graduated from Reed College and has started her first job in Portland. Her family lives in California. She has a history of asthma, which she grew out of in elementary school, and allergic rhinitis, which she manages with OTC cetirizine and nasal fluticasone.
- She would like to discuss options for birth control today. On further questioning, she has had several recent unprotected sexual encounters with 2 partners
- She also admits to having difficulty adjusting to her new job and being away from the campus environment and her close network of friends.

General considerations for all patients

- Mood: depression, suicide
- Relationships: healthy relationships/safety, STI, contraception
- Substance use: alcohol, marijuana, (e)-cigarettes, others
- Health maintenance: pap, chlamydia screening, immunizations

Example 2
Childhood-onset chronic medical condition

- Angela is a 24 year old with chronic kidney disease associated with SLE. She is following with rheumatology and nephrology, and may need a kidney transplant in the coming few years. She was diagnosed age 9 and has significant anxiety related to medical system interactions, blood draws, and imaging. Since moving to her own apartment after graduating from the local community college she has inconsistently been filling/taking medications and misses appointments frequently. She has been hospitalized three times in the last 4 months for dehydration and AKI.
- You notice she is not on a contraceptive, and she is unaware that some of her medications (ACEi) may be teratogenic. She is not familiar with any side effects of her current medications, and is uncertain on the reason for taking some of the medicines.
- She also does not know what are her emergency symptoms for seeking care/calling the office, and is unfamiliar with how/when to seek care outside of her regularly scheduled appointments in her medical home. She reports that she will call her mom or just go to the ED when she is worried about her health

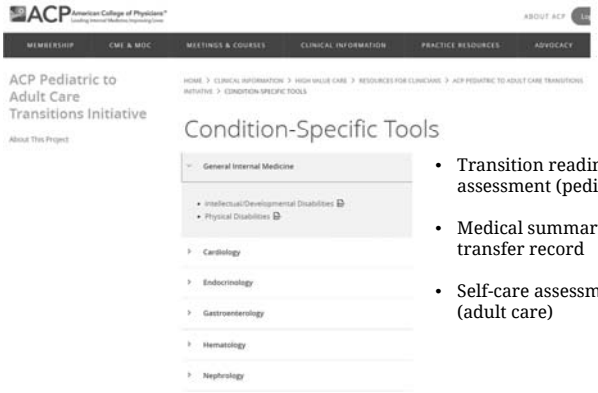


Self-management skills

- Assessment
- Navigating the health care system: filling medications, making appointments, calling for advice, insurance access and terminology
- Knowledge of condition and medications, side effects, emergency symptoms
- Other important issues to assess: housing, education, vocation, etc

My Health *Please check the box that applies to you right now.*	Yes, I know this!	I need to learn	Someone needs to do this… Who?
I know my medical needs.	☐	☐	☐
I can explain my medical needs to others.	☐	☐	☐
I know my symptoms including ones that I quickly need to see a doctor for.	☐	☐	☐
I know what to do in case I have a medical emergency.	☐	☐	☐
I know my own medicines, what they are for, and when I need to take them.	☐	☐	☐
I know my allergies to medicines and the medicines I should not take.	☐	☐	☐
I can explain to others how my customs and beliefs affect my health care decisions and medical treatment.	☐	☐	☐
Using Health Care			
I know or I can find my doctor's phone number.	☐	☐	☐
I make my own doctor appointments.	☐	☐	☐
Before a visit, I think about questions to ask.	☐	☐	☐
I have a way to get to my doctor's office.	☐	☐	☐
I know to show up 15 minutes before the visit to check in.	☐	☐	☐
I know where to go to get medical care when the doctor's office is closed.	☐	☐	☐
I have a file at home for my medical information.	☐	☐	☐
I know how to fill out medical forms.	☐	☐	☐
I know how to get referrals to other providers.	☐	☐	☐
I know where my pharmacy is and how to refill my medicines.	☐	☐	☐
I know where to get blood work or x-rays done if my doctor orders them.	☐	☐	☐
I carry important health information with me every day (e.g. insurance card, allergies, medications, emergency contact information, medical summary).	☐	☐	☐
I understand how health care privacy changes at age 18 when legally an adult.	☐	☐	☐
I have a plan so I can keep my health insurance after 18 or older.	☐	☐	☐
My family and I have discussed my ability to make my own health care decisions at age 18.	☐	☐	☐

13



- Transition readiness assessment (pediatrics)
- Medical summary/ transfer record
- Self-care assessment (adult care)

Health passport

- Use as a teaching and organizational tool
- Resources available or create your own

15

MY MEDICAL TEAM (include MD, PA, NP, PT, OT, speech, psychology, etc):

Name	Specialty	Phone number	What problem does this provider manage

MY MEDICAL PROBLEMS

Surgeries (include date)

Other important health history
Allergies: _____

Special Needs: _____

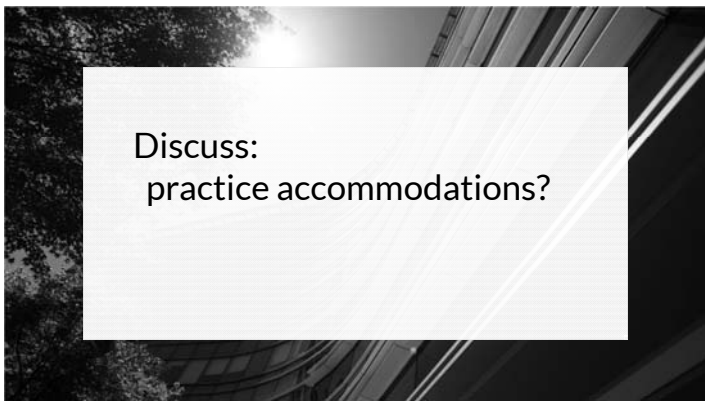
DAILY MEDICATION

Name	Dose	How many times a day	Why

Example 3
Neurodevelopmental condition

- Alyssa is a 19 year old young woman who has cerebral palsy, seizure disorder, intellectual disability, type 1 diabetes, recurrent UTIs and C diff, constipation, chronic lung disease (on BiPAP at night), contractures. She is nonverbal, nonambulatory, and is accompanied by her mother, who has dedicated her life to caring for her special needs daughter.
- You ask for documentation of guardianship/medical decision making rights, and the mother reports they cannot afford this legal process.
- Her mother wonders if there is anything you can do to keep her daughter from staying in the waiting room so long because this increases her agitation

17

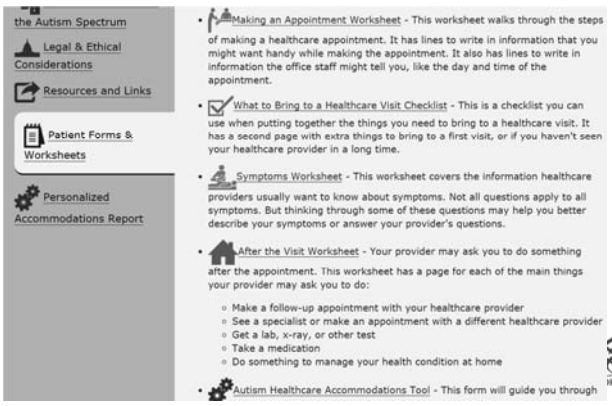


Practice accommodations

- Pre-visit calls
- Flow through clinic: waiting room
- Sensory/stimulation considerations: lights, noise, # of people talking at once
- Communication: rate of speech, use of assistive technology
- Team structure/consistent staff
- Staff knowledge about processing DME, interfacing with community organizations and support
- Working with family/supporters

Online preparatory tools

- AASPIRE Healthcare toolkit
- Down Syndrome Clinic 2 U
- More in development….



Interfacing with community

- DME
- DD services
- Community supports
- Housing
- Education
- Recreation

Oregon Family to Family Health Information Center

http://oregonfamilytofamily.org

Recreation and community life

Find ideas here for fun, travel, and being part of the community.

Social-Emotional and Mental health

Mental health includes emotional, psychological, and social well-being. It determines how we handle stress, relate to others, and make choices. Learn about resources to support and enhance your mental health.

Advanced education and training

Students are allowed to finish public high school up until the age of 21. Many people seek college or advanced training afterwards. Locate information to find and pay for education opportunities.

Transition to adult health care

Finding an adult healthcare is challenging for some. Helpful transition ideas and checklists guide the way.

Finding work

People are healthier, safer, and happier with meaningful work according to the Oregon Employment First Initiative. These resources can help you find work, navigate employment challenges, or change your work all together.

Housing choices and supports

There are choices for housing situations. Use these resources to plan for, find, and pay for housing.

Service and support animals

Animals can provide support and perform various service. Explore the type of animal to consider, learn your rights and responsibilities here.

return to top

Oregon Family to Family Health Information Center

Oregon Family to Family Health Information Center +

http://oregonfamilytofamily.org

Resources For Health Care Transition

Overview of adolescent transition to adult health care

As children get closer to adulthood, they have different needs. By the time they are 18 they need a solid transition plan, even if they still need support. Find resources for patients aged 12-25.

Got Transition.org

Teen's Rights to Access, Confidentiality, and HIPAA

Maternal Child Health Information on Care for Adolescents and Young Adults

American College of Physicians: Condition-specific transition

Tools to use with transition-age youth and families

Support your patients and their families with these helpful resources.

Transition Planning Checklist

Preparing Families for Transition

OR Dept. of Education Transition Planning

National Gateway to Self-Determination

Transition Readiness Assessment (Health)

Adolescent Autonomy Checklist (SPAN NJ)

Legal stuff

- Medical decision making rights
- Adult foster care
- Guardianship
- Supported decision making
- Consent
- Privacy

The Arc Oregon

DISABILITY RIGHTS OREGON

HOME WHO WE ARE WHA

Home Need help? What we do Who we a

GAPS GUARDIANSHIP ADVOCACY & PLANNING SERVICES

Guardianship

Disability Rights Oregon works to protect individuals against guardianships whe there is abuse or neglect. In addition, DRO can intervene when a respondent o protected person's civil rights are being violated due to the guardianship. DRO receives pleadings in guardianship and conservatorship, which we review to ens that the civil rights of the respondent/ protected person are being upheld.

Publications

DRO-Guardianship_Handbook

www.autismspeaks.org

Special Needs Financial Planning

Resources to help you and your family plan for the future.

Special Needs Financial Planning Tool Kit

This comprehensive guide covers all of the critical topics related to planning for the future.

Financial Planning App

Learn more and organize your plans with this helpful app.

Financial Assistance

A list of resources available to help people looking for financial support.

Resources

- See Handout

Discuss:
medical and psychiatric comorbidities

Medical comorbidities: Specific to neurodevelopmental disorders

- Sleep problems
- Constipation
- GERD
- Seizures/neurologic manifestations
- Headache/visual disturbance
- Behavioral/psychiatric
- Other team members: speech, OT, PT, nutrition

Psychiatric comorbidities: Specific to neurodevelopmental disorders

- Anxiety
- Depression
- ADHD
- Others: OCD, tics, bipolar

- Listen carefully to description of behavior
  - Diagnosis of bipolar in a 29 year old with CP, ID who had periodic episodes of insomnia (several nights of no sleep) associated with flares of aggression. Started mood stabilizer and sx subsided.
  - New seizures in a 17 year old with ASD with changes in behavior and daytime functioning (long pauses) → staring spells

Summary

- Diversity of patients (3 large 'buckets')
  - Each patient will have unique needs
  - Patients with neurodevelopmental disorders have a high need for support

- Many resources exist; don't re-create work that has already been done and is freely available

Discuss:
how does this apply in your clinical setting?

Brainstorm:
what is one concrete step you can propose next week to move these issues forward in your setting?

Review objectives

- Describe specific steps that a primary care provider can take to overcome the barriers faced by adults with intellectual and physical disabilities and chronic diseases of childhood in seeking medical treatment in an adult care setting
- Create a plan that will implement at least one change in practice to accommodate patients with intellectual and physical disabilities and chronic diseases of childhood

OHSU

OHSU

Thank You

Questions?
hasanr@ohsu.edu

Pregnancy, Disability, and Woman's Decisions

An eight part series on pregnancy and pregnancy decisions for women with intellectual disability and Autistic women.

VIDEOS RESOURCES ABOUT CONTACT

Videos

This is an eight part series on pregnancy and pregnancy decisions for women with intellectual disability and Autistic women.

Sexually transmitted infections in primary care: challenges and opportunities

OSHU Primary Care Conference 2019
Tim W. Menza, MD, PhD
Medical Director, HIV/STD/TB
Oregon Health Authority

Objectives

- Typical and not-so-typical presentations of STI
- Epidemiology of bacterial STI in Oregon
- Diagnostics for STI
- Empiric and diagnosis-driven treatment recommendations

Case. A 24-year-old woman with vaginal bleeding and dysuria

- Presents to urgent care clinic
- Noticed spotting after intercourse over the past 2 days
- Some dysuria, has not noticed change in vaginal discharge
- Positive pregnancy test about 3 months ago; has not yet established prenatal care
- Sex with men, reports only one partner, denies anal sex
- No substance use

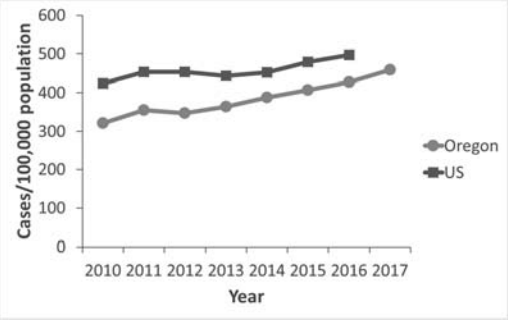
Next steps

- Pelvic exam
- Document IUP with ultrasound
- Urinalysis
- Saline and KOH preps
- First void urine or endocervical swab or vaginal swab for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*
- Prenatal care

Diagnostic work-up

- Cervix appears reddened, but without friability or discharge
- IUP on ultrasound
- Wet mount +WBC but no clue cells, no trichomonads
- KOH prep without fungal elements
- UA with some RBCs, negative nitrite, negative LE, no WBC
- Endocervical swab CT NAAT positive

Chlamydia positivity in the U.S. and Oregon



Treatment options for Chlamydia

RECOMMENDED THERAPY

Azithromycin 1 g PO x 1 **OR** **Doxycycline 100 mg PO BID x 7 days**

ALTERNATIVE REGIMENS:
Erythromycin base 500 mg PO QID for 7 days **OR**
Erythromycin ethylsuccinate 800 mg PO QID for 7 days **OR**
Levofloxacin 500 mg PO QD for 7 days **OR**
Ofloxacin 300 mg PO BID for 7 days

Expedited partner therapy

Study Outcome	Prevalence/Rate Ratio (95% CI)	*p*-Value
Chlamydia positivity in women ages 14–25 y	0.89 (0.77–1.04)	0.15
Reported gonorrhea incidence in women	0.91 (0.71–1.16)	0.45
Combined chlamydia positivity and gonorrhea incidence	0.90 (0.80–1.01)	0.06

- There is no evaluation of the partner by the provider
- Recommended for heterosexual men and women
- Especially important when there is a concern that the partner will not present for evaluation and treatment
- Goal: prevent reinfection and, in this case, prevent pre-term delivery

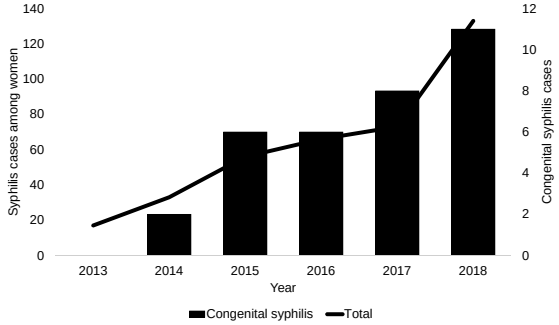
Golden et al, PLOS One 2015.

EPT regimens

Partners of patients diagnosed with chlamydia:
- Azithromycin (Zithromax*) 1 gram orally once

Partners of patients diagnosed with gonorrhea:
- Cefixime (Suprax*) 400 mg orally once **AND**
- Azithromycin (Zithromax*) 1 gram orally once

Syphilis among women and congenital syphilis are increasing in Oregon



Current recommendations for syphilis screening in pregnancy in Oregon

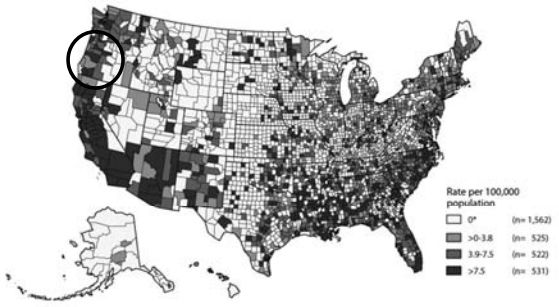
Triple screening among pregnant women in Oregon
At first prenatal visit
Third trimester
At delivery

- Based on 2017 data, if pregnant women in Oregon were screened only at the first pre-natal visit, we would miss 22% of syphilis cases

CDC and ACOG Prenatal Syphilis Screening Recommendations

"…in communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' EGA and at delivery."

Primary and secondary syphilis by county, United States, 2017



Case. A 45-year-old man with 2-3 days of rectal pain

- In addition to pain, he feels ill, is constipated, and he reports pain initiating urinary stream
- Reports blood on the toilet paper when he tries to defecate
- Reports condomless receptive anal sex with another man 2 weeks prior to the onset of symptoms
- Last HIV, RPR, GC/CT testing was negative 4 weeks ago; he reports having had rectal Chlamydia in the past
- He is not on pre-exposure prophylaxis (PrEP)

What do you do next?

- Pharyngeal and GU exams (including inguinal lymph nodes)
- Anoscopy to visualize the rectal mucosa
- Rectal swabs for gonococcal and Chlamydial nucleic acid amplification testing (NAAT)
- Rectal swab for HSV DNA PCR (**do not** send serologies!)
- Wrap-around testing: HIV, RPR, pharyngeal GC, urine GC/CT
- Any other testing?

Anoscopy reveals…

- Tender, inflamed rectal mucosa
- A 2-cm well-demarcated ulcer with smaller ulcers that you note as you slowly remove the anoscope
- Some blood on the swabs after you take your samples

What is on your differential for sexually transmitted proctitis?

- *Neisseria gonorrhoeae*
- *Chlamydia trachomatis*
  - Serovars D-K
  - Serovars L1-L3 (etiologic agents of lymphogranumloma venereum)
- *Treponema pallidum*
- Herpes simplex virus type 1 or 2
- Other considerations: Campylobacter, Shigella, Giardia, *Entamoeba histolytica* (if primary presentation is diarrheal disease), CMV in immunocompromised people

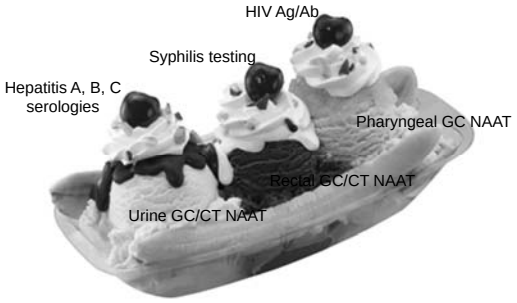
What course of empiric treatment do you recommend?

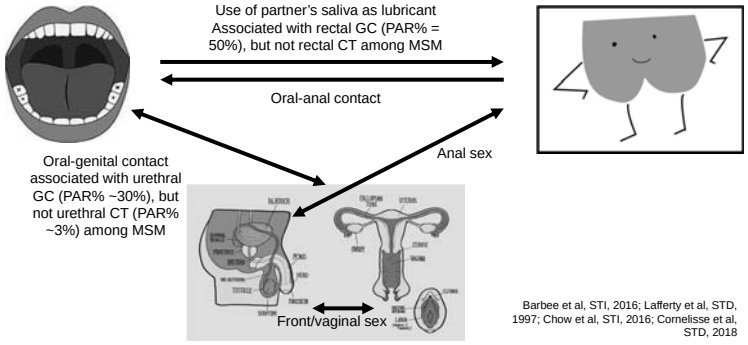
Empiric therapy for sexually transmitted proctitis
Ceftriaxone 250 mg IM x 1 *PLUS*
Doxycycline 100 mg PO BID for 7-21 days (why am I including a range here?)
Valacyclovir 1000 mg PO BID for 10 days (in a patient with rectal/anal ulcers on exam)

Diagnostic tests return…

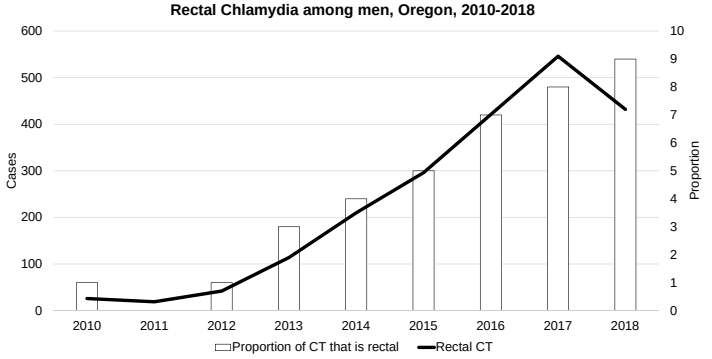
- Rectal HSV-2 DNA detected
- Rectal GC NAAT positive
- Rectal CT NAAT negative
- RPR negative
- HIV Ag/Ab test negative

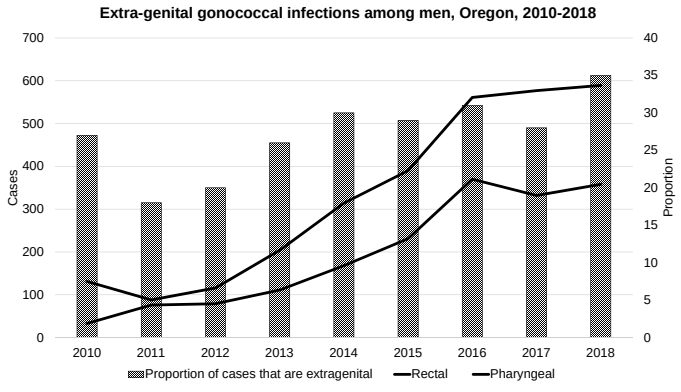
Complete, integrated STI screening



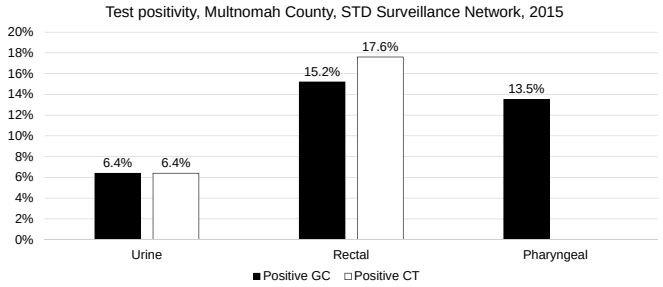


Barbee et al, STI, 2016; Lafferty et al, STD, 1997; Chow et al, STI, 2016; Cornelisse et al, STD, 2018

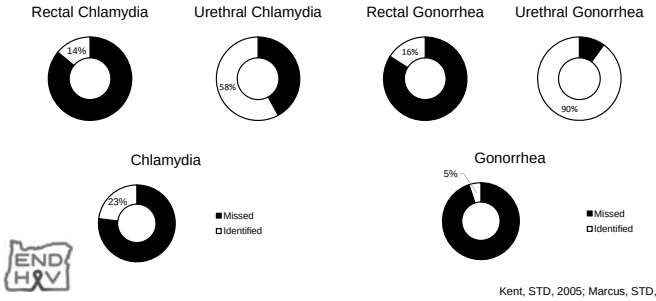




MSM are more likely to have extragenital GC/CT than urethral GC/CT

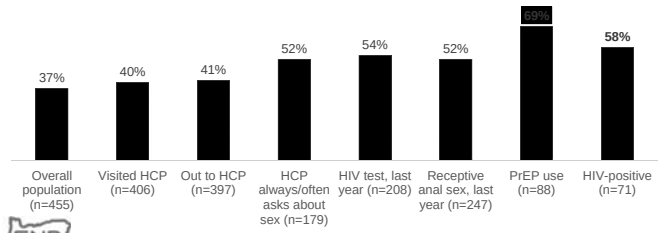


Most extra-genital GC/CT infections are asymptomatic among MSM

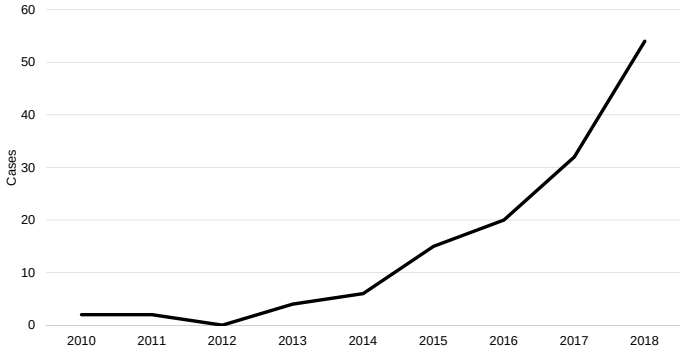


Kent, STD, 2005; Marcus, STD, 2011.

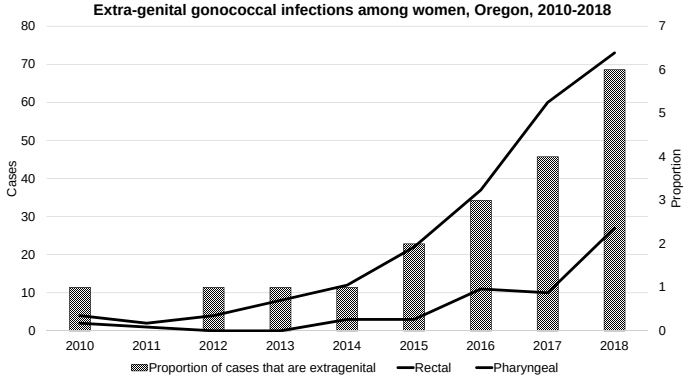
Screening for rectal STI among MSM is not universal, NHBS, Portland, 2017



Rectal Chlamydia among women, Oregon, 2010-2018



Extra-genital gonococcal infections among women, Oregon, 2010-2018



Up to 50% of rectal infections among heterosexual women are missed with urogenital screening only

Sample	Rectal CT	CT missed	Rectal GC	GC missed
Baltimore STD clinics	8.6%	13.8%	2.9%	30%
LA STD clinics	3.0%	25%	14.6%	18.5%
Adult film performers	17%	15%	4%	15%
STD clinics in IL, AL	16.5%	23%	32.1%	16%
Miami-Dade STD clinics	13.4%	6%	17.5%	38%
Alabama, STD and HIV clinics	23.1%	23.3%	5.6%	15.8%
US Lab Corp data (combined GC/CT)	10.8%	46.5%		

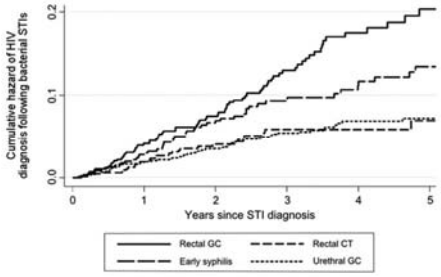
Trebach *et al. Sex Transm Dis*, 2015; Javanbackht *et al. Sex Transm Dis*, 2012;Rodriguez-Hart *et al. Sex Transm Dis,* 2012; Bachmann *et al. J Clin Micro,* 2010; Hunte *et al. Int J STD AIDS*, 2010; Bachmann *et al. Sex Transm Dis*, 2009; Tao *et al. CID*, 2018.

Collection kits for GC/CT NAAT

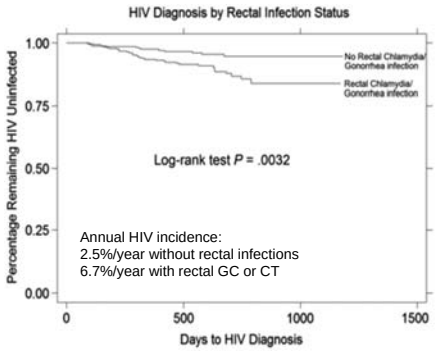
Unisex swab specimen collection kit for rectal, pharyngeal, and endocervical samples

Vaginal swab specimen collection kit

Bacterial STI increases the risk of HIV acquisition



Katz et al, STD, 2016.



Pathela *et al. CID*, 2013.

This patient is a PrEP candidate

Use of antiretroviral medication before exposure to HIV to reduce the risk of infection

A combination of tenofovir (TDF) plus emtricitabine (FTC)

- Daily dosing
- Few drug interactions
- Safe and well-tolerated

FDA approved in 2012

Who else can benefit from PrEP?

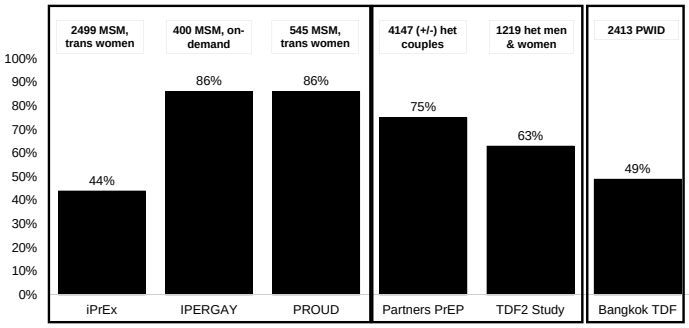
US Public Health Service
PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES – 2017 UPDATE
A CLINICAL PRACTICE GUIDELINE

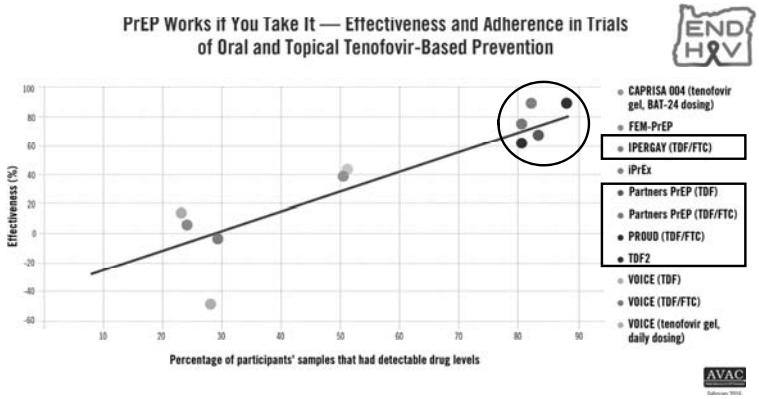
CDC

HIV-negative, plus

- HIV-positive partner(s)
- History of syphilis, chlamydia, or gonorrhea
- Condomless anal or vaginal sex
- Multiple sex partners
- Shared injection equipment
- Methamphetamine use
- Transactional sex
- High-prevalence area or sexual network
- Repeated use of nPEP

How effective is PrEP at preventing HIV?





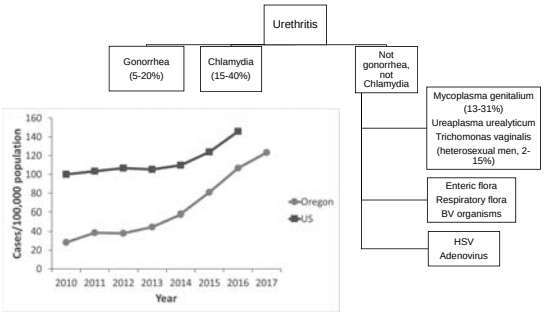
When taken regularly, PrEP is >85-90% effective in preventing HIV infection

For **PrEP**, number needed to treat to prevent 1 HIV infection = 13-60
For **statins**, number needed to treat to prevent 1 CV event = 50-130

Case. A 38-year-old man with persistent urethritis

- Presented 3 weeks ago with penile discharge, dysuria, and urethral itching
- Treated empirically with azithromycin 1 gram PO x 1, symptoms did not improve
- Urine GC/CT NAAT returned negative, UA 5-10 WBC, +LE
- Subsequent treatment with a 7-day course of doxycycline 100 mg BID with minimal improvement
- Sexually active as a top and bottom with multiple male partners
- HIV-negative on pre-exposure prophylaxis

Differential diagnosis of urethritis



Recommended treatment for an initial episode of NGU

RECOMMENDED THERAPY

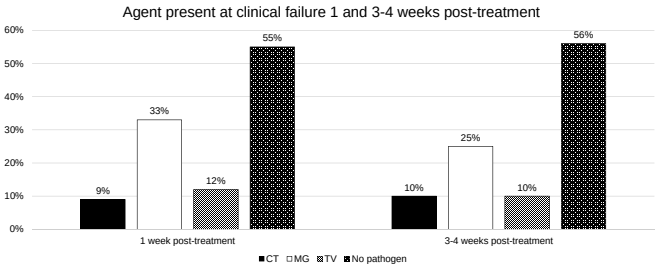
Azithromycin 1 g PO x 1 **OR** **Doxycycline 100 mg PO BID x 7 days**

ALTERNATIVE REGIMENS:
Erythromycin base 500 mg PO QID for 7 days **OR**
Erythromycin ethylsuccinate 800 mg PO QID for 7 days **OR**
Levofloxacin 500 mg PO QD for 7 days **OR**
Ofloxacin 300 mg PO BID for 7 days

Reasons for lack of symptom resolution

- Re-infection
- Adherence to treatment course
- Drug resistance
- Post-infectious immunologic response
- Complicated infection

Overall, 13% of men with NGU experience clinical failure



Seña et al, JID 2012.

Resistance patterns complicate treatment

- CT clearance rate 95% with doxycycline v 77% for azithromycin
  - A more recent study shows a 93.4% clearance rate for CT treated with azithromycin
  - Another showed no difference in treatment effectiveness
- Doxycycline is only 20-30% effective against MG while azithromycin is >70% effective; however, more recent studies show low clearance rates (30-40%) for both drugs
- A large survey of MG specimens in Denmark showed that 40% were resistant to macrolides

Bachmann et al, CID 2015.

Persistent or recurrent NGU

- Completed initial treatment, no history of re-exposure

If azithromycin used first, then treat with moxifloxacin 400 mg PO QD x 7 days

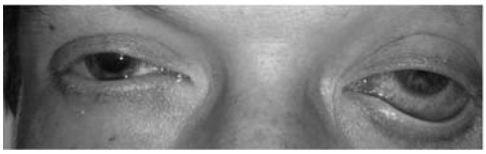
If doxycycline used first, then treat with azithromycin 1 gram PO x 1

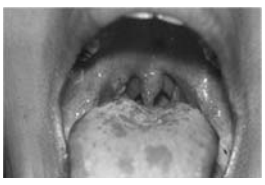
PLUS

For men who have sex with women:
Metronidazole 2 grams PO x 1
OR
Tinidazole 2 grams PO x 1

Case. A 33-year-old man with sinusitis and a rash

- Six weeks ago, presented with sore throat and tinnitus, dx with sinusitis, tx with abx x 7 days
- Now with blurry vision
- Worsening eczema over the past 2 months
- Ex-Navy, extensive travel
- Two female partners in the past year
  - Fiancée and a women he refers to as his fiancée's girlfriend



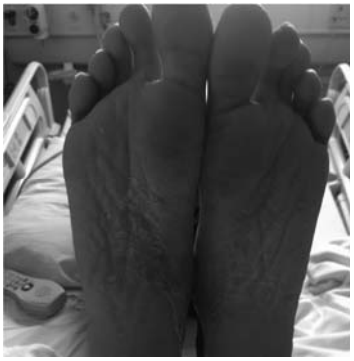


Emergent ophthalmologic exam

- Panuveitis
- Bilateral acute retinal necrosis

What is the most likely diagnosis?

- Hyperkeratotic plaques with collarette scales on palms and soles (Biett collarettes)
- Mucous patches
- Ocular symptoms
- Tinnitus
- Recalls having a chancre on his penis



Diagnostic testing returns…

- HIV negative
- RPR 1:512
- TPPA positive
- GC/CT urine and pharyngeal NAAT negative
- Admitted for LP and IV PCN
  - VDRL 1:2
  - CSF WBC 75 (78%L)
  - No improvement of vision at discharge, prognosis for future improvement is guarded

A Cluster of Ocular Syphilis Cases — Seattle, Washington, and San Francisco, California, 2014–2015

Sophie Woolston, MD[1]; Stephanie E. Cohen, MD[2,3]; Robyn Neblett Fanfair, MD[4]; Sarah C. Lewis, MD[3]; Christina M. Marra, MD[5]; Matthew R. Golden, MD[1,6]

Morbidity and Mortality Weekly Report

Ocular Syphilis — Eight Jurisdictions, United States, 2014–2015

Sara E. Oliver, MD[1,2]; Mark Aubin[3]; Leah Arwell, MPH[4]; James Matthias, MPH[4,5]; Anna Cope, PhD[3,6]; Victoria Mobley, MD[6]; Alexandra Goode, MSc[7]; Sydney Minnerly, MA[8]; Juliet Stoltey, MD[9]; Heidi M. Bauer, MD[3]; Robin R. Hennessy, MPH[3,10]; Dawne DiOrio, MPA[3,11]; Robyn Neblett Fanfair, MD[12]; Thomas A. Peterman, MD[3]; Lauri Markowitz, MD[2]

Ocular syphilis

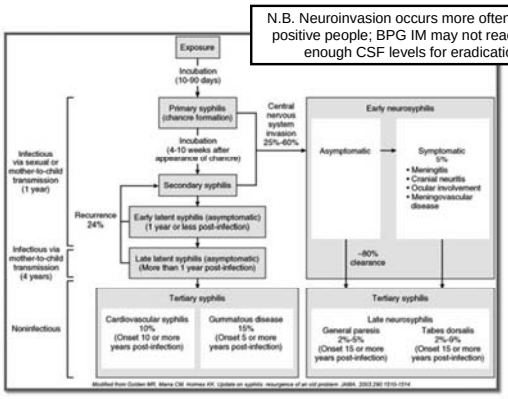
- No classic presentation
- Occurs at ANY stage of syphilis
  - Most often seen with secondary syphilis
- Managed as neurosyphilis
  - LP may be negative in ocular syphilis
- Visual loss can be reversible if treated early, but there have been cases of irreversible blindness

Treatment of ocular and neurosyphilis

Recommended Regimen
Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10-14 days

NB. For patients with late syphilis, benzathine penicillin 2.4 million units can be given once a week for up to three weeks after completion of neurosyphilis treatment.

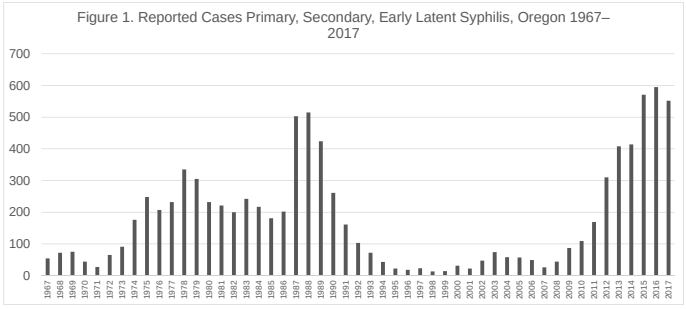
N.B. Neuroinvasion occurs more often in HIV-positive people; BPG IM may not reach high enough CSF levels for eradication

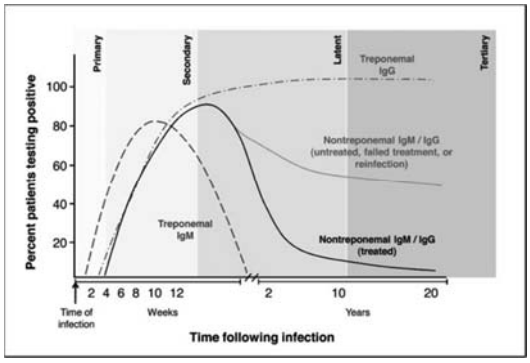


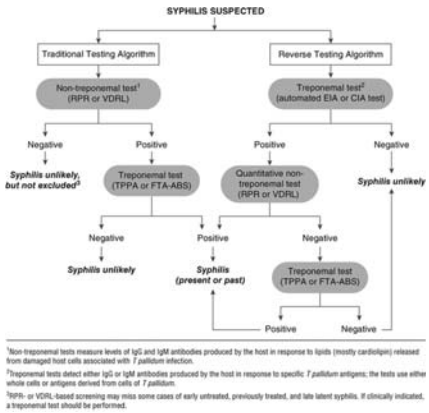
Neurosyphilis review of systems

- General: headache, fever, fatigue, weakness, dizziness
- EYE: eye pain, redness, loss of vision, double or blurred vision, photophobia, flashing lights/spots
- EAR: tinnitus, hearing loss
- GI: nausea/vomiting
- MSK: neck stiffness, muscle weakness
- NEURO: stroke-like symptoms, seizure, cranial nerve deficits, weakness, paresthesia/sensation change, gait changes, behavior or personality change, dementia

Fifty years of syphilis in Oregon







Examples of interpretation of the reverse algorithm

T1 Interpretation and recommended follow-up testing with the reverse sequence screening algorithm for syphilis

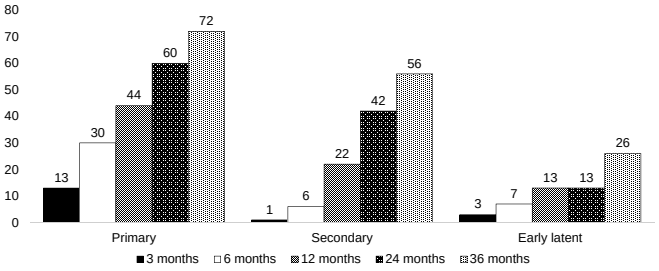
CASE	RESULT OF TREPONEMAL SCREENING TEST[1]	RESULT OF NON-TREPONEMAL TEST (E.G., RPR)	RESULT OF SECOND TREPONEMAL TEST (E.G., TP-PA)	INTERPRETATION
1	Negative	N/A	N/A	Negative for syphilis. No further testing required, unless clinically indicated.
2	Positive	Negative	Positive	Possible past, successfully treated syphilis. Thorough review of history required to rule-out early or latent syphilis.
3	Positive	Positive	N/A	Likely untreated or recently treated syphilis. Follow CDC treatment guidelines.[2]
4	Positive	Negative	Negative	Likely false-positive screening test. No further testing required, unless clinically indicated.

N/A, not applicable
1. CIA, chemiluminescence immunoassay; EIA, enzyme immunoassay; MFI, multiplex flow immunoassay
2. http://www.cdc.gov/std/treatment/2010/

Treatment of syphilis

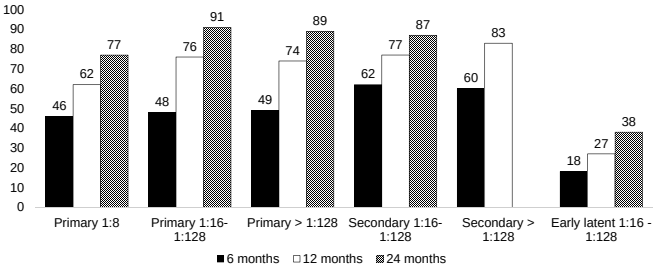
	Recommended Treatment	Alternative Treatment if Penicillin Allergic
Primary/secondary/ early non-primary non-secondary	Bicillin 2.4 million units in a single dose	Doxycycline 100 mg twice daily for 14 days
Late/unknown duration (more likely among heterosexuals)	Bicillin 7.2 million units as three doses of 2.4 million units each at 1-week intervals	Doxycycline 100 mg twice daily for 28 days

When does the RPR revert back to non-reactive?



Romanowski et al, 1991.

When should I expect a 4-fold decrease in RPR?



Romanowski et al, 1991.

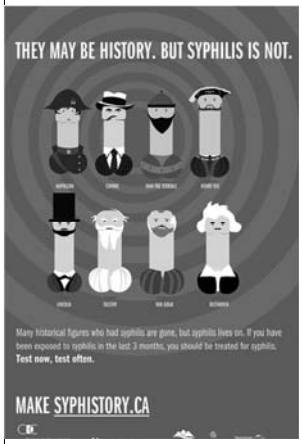
Follow-up (this works for all stages)

- Ideally, RPR every 3-6 months until at least a 4-fold reduction in RPR after treatment
  - Some patients may remain sero-fast with low-level titers after treatment (RPR ≤1:8)
- Thereafter, screen according to risk of re-infection with RPR only
- If RPR has not decreased 4-fold in 12 months:
  - Low level infection with *T. pallidum*
  - Variability in host response to infection
  - Confounding non-treponemal inflammatory conditions
- What to do
  - Consider treatment failure and retreat (often done in practice)
  - Consider neuro-invasion and perform CSF examination

Seña et al, CID 2013.

What I hope you learned

- EPT should be standard practice among heterosexuals with Chlamydia or gonorrhea
- Syphilis in women and, thus, congenital syphilis are increasing sharply
  - Screen pregnant women at first prenatal visit, 3rd trimester, and delivery
- Integrated HIV/hepatitis/GC/CT screening should be routine practice
- Extragenital infections are common and frequently missed among MSM and women
  - Rectal infections carry a substantial risk of HIV acquisition
  - Rectal GC and syphilis are clear indications to start PrEP
- Persistent NGU is not uncommon
- Have a high level of suspicion for neuro and ocular syphilis
- Syphilis screening algorithms and follow-up
  - Syphilis is a complicated multi-system disease



Sexually transmitted infections are often more nuanced than we think.

If you need guidance call or email.

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971-673-0150

The Cardiovascular Effects of E-Cigarettes and Marijuana:

Healthier Alternative or Too Good to Be True?

Tina M. Kaufman, PhD, PA-C
Clinical Assistant Professor, Preventive Cardiology
Clinical Supervisor, Cardiac Rehabilitation

Objectives

- Emergence of e-cigarettes
- Use of e-cigarettes
- Cardiovascular effects of e-cigarettes
- Cardiovascular effects of marijuana
- What do I tell my patients?

Warning!!!

- **Caution…you are about to enter a (relatively) evidence free zone**
- Proceed at your own risk

Ms Smith, a 52 yo woman with diabetes, hypertension comes to see you for follow up. She started using e-cigarettes to quit smoking and has decreased her tobacco use from 1 ppd to 1/4 ppd. Which of the following is true?

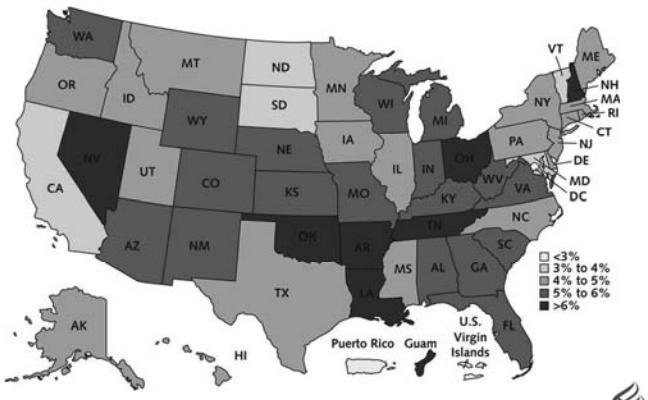
A. E-cigarettes have no known adverse cardiovascular effects
B. E-cigarettes contain same amount of toxins as conventional cigarettes
C. E-cigarettes are safe to use indefinitely if it keeps her from smoking
D. E-cigarettes are likely not as effective as other FDA approved medications for smoking cessation

Emergence of E-Cigarettes

- Modern e-cigarette was invented in 2003 by Chinese pharmacist, and as of 2015 most e-cigarettes are made in China[1]
- Deliver nicotine through aerosol of chemically complex ultrafine particles
- First sold in US in 2007 their global use has risen exponentially[2]
- As of 2014, there were 466 brands of e-cigarettes, and > 7,000 flavors[3]
- Global e-cigarettes market value is estimated to reach up to $30 billion by the end of 2024 from approximately $13 billion in the year 2017[4]

1. UCSG: Center for Tobacco Control Research and Education. Retrieved from: http://escholarship.org/uc/item/13p2b72n
2. Tob Control. 2013 Jan;22(1):19-23
3. The Wall Street Journal. February 20, 2015
4. https://www.envisionintelligence.com/industry-report/global-e-cigarette-market/

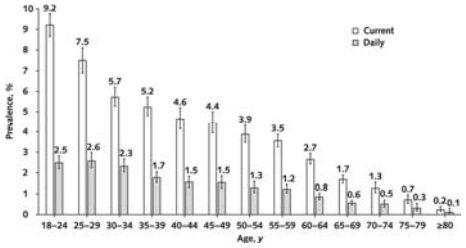
Prevalence of Current e-Cigarette use in U.S. Adults



Ann Intern Med. 2018. DOI: 10.7326/M17-3440

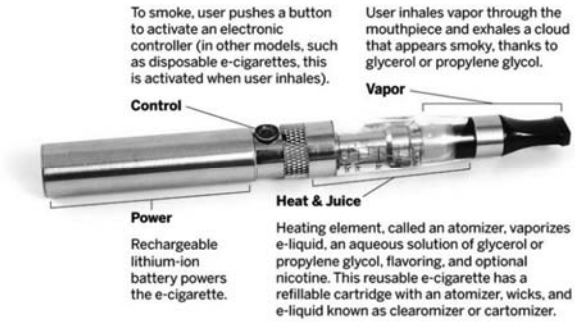
Prevalence of Current e-Cigarette Use in US in 2016

- 4.5% of U.S. adults us e-cigarettes
- Adults younger than 35 years accounted for more than half of all e-cigarette users
- Highest prevalence among men; lesbian, gay, bisexual, and transgender persons; those who were unemployed; and those with chronic disease



Ann Intern Med. 2018. DOI: 10.7326/M17-3440

Anatomy of an e-Cigarette



Examples of different e-cigarette products

Product	Description	Some Brands
Disposable e-cigarette	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing aerosol. Sometimes called an e-hookah.	NJOY OneJoy, Aer Disposable, Flavorvapes
Rechargeable e-cigarette	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and /or how many puffs may be taken consecutively.	Blu, GreenSmoke, EonSmoke
Pen-style, medium-sized rechargeable e-cigarette	Larger than a cigarette, often with a higher capacity battery, may contain a prefilled cartridge or a refillable cartridge (often called a clearomizer). These devices often come with a manual switch allowing to regulate length and frequency of puffs.	Vapor King Storm, Totally Wicked Tornado
Tank-style, large-sized rechargeable e-cigarette	Much larger than a cigarette with a higher capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.	Volcano Lavatube

Rachel Grana et al. Circulation. 2014;129:1972-1986

E-Cigarettes

- Reasons for using e-cigarettes:
  - Trying to quit smoking
  - Perceived as healthier
  - Save Money
  - Circumvent smoking restrictions
  - Recreational
  - Majority of users still smoke tobacco (dual use)[1]
    - May delay or deter quitting?

Circulation. 2014;129:1972-1986

E-Cigarettes

- As of August 2016, the US FDA extended its regulatory power to include e-cigarettes:
- Manufacturers of newly regulated tobacco products that were not on the market as of February 15, 2007, will:
  - Have to show that products meet the applicable public health standard set by the law
  - Receive marketing authorization from the FDA
  - Continue selling their products for up to two years while they submit—and an additional year while the FDA reviews—a new tobacco product application
- As of July 2017, the FDA is giving e-cigarette makers four more years to comply
- So still unregulated for the next 5 years

E-Cigarettes Healthier?

E-Cigarettes

Advantages:

- Do not contain tar or carbon monoxide
- Lower levels of toxins than cigarette smoke

Concerns:[1,2,3]

- Other cancer causing ingredients
- Polypropylene glycol (when heated→formaldehyde)
- Diacetyl (flavoring agent→"popcorn lung")[3]
- 5 minutes of use→significant increase air flow resistanceUnknown long term risks of many of the toxins present
- Strong evidence that frequent low or short-term levels of exposure to ultrafine particles (tobacco smoke or air pollution) can increase the risk of cardiovascular and respiratory disease and death

1. Circulation. 2014;129(19):e490-492
2. Chest. 2012; 141: 1400-1406
3. Environ Health Perspect; DOI:10.1289/ehp.1510185

Levels of Toxicants in E-Cigarette Aerosol Compared With Nicotine Inhaler and Cigarette Smoke

Toxicant	Range in Content in Aerosol From 12 E-Cigarette Samples per 15 Puffs*	Range in Content in Conventional Cigarette Micrograms in Mainstream Smoke From 1 Cigarette	Content in Nicotine Inhaler Mist per 15 Puffs*
Formaldehyde, µg	0.2–5.61	1.6–52	0.2
Acetaldehyde, µg	0.11–1.36	52–140	0.11
Acrolein, µg	0.07–4.19	2.4–62	ND
o-Methylbenzaldehyde, µg	0.13–0.71	...	0.07
Toluene, µg	ND–0.63	8.3–70	ND
p,m-xylene, µg	ND–0.2	...	ND
NNN, ng	ND–0.00043	0.0005–0.19	ND
NNK, ng	ND–0.00283	0.012–0.11	ND
Cadmium, ng	ND–0.022	...	0.003
Nickel, ng	0.011–0.029	...	0.019
Lead, ng	0.003–0.057	...	0.004

 Tob Control. 2014;23:133–139

E-Cigarettes and Toxicants

- Some cardiovascular toxicants present in tobacco smoke, eg, particulate matter and carbonyls such as formaldehyde, acetaldehyde, acetone, acrolein, and butanol, are also present in e-cigarettes[1]
- By themselves, these can increase cardiovascular disease (CVD) risk by affecting blood pressure regulation, promoting coagulation, and accelerating the formation of atherosclerotic lesions[1]

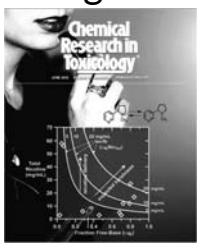
JAMA Cardiol. 2017;2(3):237-238. doi:10.1001/jamacardio.2016.5550

Tobacco-Related Toxicants

- E-cigarette use only results in measurable exposure to tobacco-related toxicants
- Compared with cigarette smoking, concentrations of tobacco-related toxicants among e-cigarette–only users were much lower
- Dual users exhibited higher concentrations of exposure to nearly all tobacco-related toxicants compared with cigarette-only smokers
- 82% of dual users reported daily cigarette smoking
- Although E-cigarettes are sources of exposure to toxicants that are linked to illness, the degree to which e-cigarette use may facilitate or hinder the development of disease downstream remains unknown

JAMA Netw Open. 2018;1(8):e185937. doi:10.1001/jamanetworkopen.2018.5937

E-Cigarette Nicotine Free Base



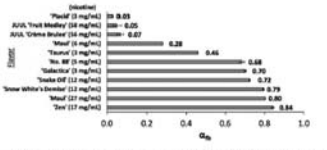


Figure 3. Free-base nicotine fraction (α_{fb}) in commercial e-liquids as an average using aromatic protons H_a and H_b. The ranges between free base values are indicated. Nicotine amounts as indicated to the right of each name were determined by NMR integrations, relative to the PG and GL resonances.

DOI: 10.1021/acs.chemrestox.8b00097 Chem. Res. Toxicol. 2018, XXX, XXX−XXX

- Nicotine is often predominately in its free-base form, which can provide a harsh and unpleasant vaping experience at high nicotine levels
- JUUL adds benzoic acid to its e-cigarette liquids, which reduces free-base nicotine proportion while maintaining the total nicotine delivery

Currently 219 candy flavors – bubble gum, cotton candy

"Juul Suspends Selling Most E-Cigarette Flavors in Stores"

- Facing mounting government pressure and a public backlash over an epidemic of teenage vaping, Juul Labs announced that it would suspend sales of most of its flavored e-cigarette pods in retail stores and would discontinue its social media promotions[1]
- But then the FDA, which previously threatened a ban on flavored e-cigarettes , said it would allow stores to continue selling such flavored products, but only from closed off-areas that would be inaccessible to teenagers[2]
- So now, Juul Labs said it would allow stores to continue selling such flavored products, but only from closed off-areas that would be inaccessible to teenagers[2]
- **Some 3.6 million people under 18 reported using e-cigarettes**

1. New York Times, November 13, 2018
2. New York Times, November 15, 2018

Effects on Endothelial Function

- Short-term exposure of endothelial cells to flavoring compounds used in *tobacco products* have adverse effects on endothelial cell phenotype that may have relevance to cardiovascular toxicity

Arteriosclerosis, Thrombosis, and Vascular Biology. 2018; ATVBAHA.118.311156

E-Cigarettes and Smoking Cessation

- Only a few well-designed research studies that examined their effectiveness in smoking cessation or reduction, and, in those studies, quit rates were modest and lower than those of commonly used smoking cessation therapies[1,4]
- Concerns have also been raised regarding increased nicotine dependence with e-cigarette use, which may eventually promote tobacco use[2,5]
- Light smoking, even 1 to 4 cigarettes per day, is associated with markedly elevated risk of cardiovascular disease[3]

1. Ann. N.Y. Acad. Sci. 2015; 1340: 65–74
2. Am J Respir Crit Care Med. 2014 Sep 15;190(6):611-8
3. *Tob Control. 2005;14:315–320*
4. Otolaryngol. Head Neck Surg. 2014;151: 381–393
5. NEJM. January 2019. DOI: 10.1056/NEJMoa1808779

E-Cigarettes and Smoking Cessation

- The 2014 report of the US Surgeon General concluded:
- "Reducing the number of cigarettes smoked per day is much less effective than quitting entirely for avoiding the risks of premature death from all smoking-related causes of death
- Use of electronic cigarettes by cigarette smokers to cut down on the number of cigarettes smoked per day is likely to have much smaller beneficial effects on overall survival compared with quitting smoking completely"

Centers for Disease Control and Prevention, National Center on Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014

E-Cigarettes and the Heart

- Study of habitual e-cigarette users and nonuser control individuals (N=42) from 2015 to 2016 at the University of California, Los Angeles
- Heart rate variability associated with a shift toward sympathetic predominance ("fight or flight response") and decreased vagal tone
- Increased systemic oxidative stress
- Not attributable to nicotine (levels undetectable)

JAMA Cardiol. Published online February 1, 2017. doi:10.1001/jamacardio.2016.5303

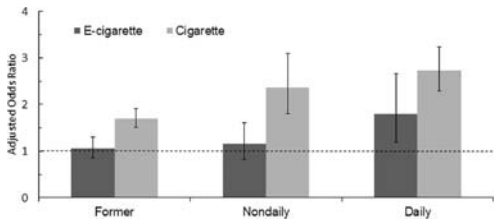
E-Cigarettes and the Heart

- Study in 40 healthy subjects (20 smokers and 20 nonsmokers), matched for age and sex
- In smokers and nonsmokers without cardiovascular disease, both tobacco and e-cigarettes have unfavorable effects on markers of oxidative stress and ability of arteries to dilate after single use
- The bioavailability of NO (natural vasodilator) was also reduced by e-smoking
- The effects of e-cigarettes were less pronounced than those caused by traditional tobacco cigarettes

Chest. 2016; 150(3): 606-612

E-Cigarette Use and Risk of MI

- Odds of having had a heart attack was about 1.7 for daily e-cigarette users compared with subjects who had never used e-cigarettes (independent of and in addition to the risks associated with smoking and other risk factors)[1]
- Dual use of e-cigarettes and conventional cigarettes—the most common use pattern among e-cigarette users—was more dangerous than using either product alone
- Neither former nor some day e-cigarette use were associated with increased risk of heart attack
- Increased risk of MI and stroke, despite users being younger, having lower BMI, and lower prevalence of diabetes[2]



1. American Journal of Preventive Medicine. October 2018. Vol 55(4): 455-461
2. American Stroke Association International Stroke Conference, Jan 2019

Challenges with Current Studies

- E-cigarettes largely unregulated, manufactured by numerous companies
  - Great variation in their contents
  - In some cases are not consistent with labeling
- Most studies did not differentiate between use of first-, second-, third-, or later-generation e-cigarette devices used participants – can be important in differential exposure to nicotine and toxicants among e-cigarette users in other studies
- Makes it very difficult to evaluate the general safety and health risks of E-cigarettes

Otolaryngol. Head Neck Surg. 2014; 151: 381–393

E-Cigarettes: What We Know

- Definitive data on facilitating smoking cessation are lacking, but likely lead to dual use rather than cessation
- E-cigarette aerosol may contain fewer toxicants than cigarette smoke
- Not FDA approved
- Not yet regulated (will likely start in ~~2019~~, 2023?)
- Studies evaluating whether e-cigarettes are less harmful than cigarettes are still inconclusive
- The health impact of e-cigarettes, for users and the public, cannot be determined with currently available data

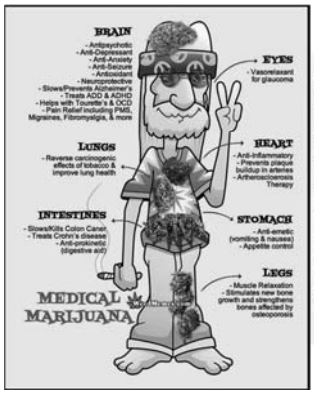
Tobacco Control 2014;23:ii36-ii40

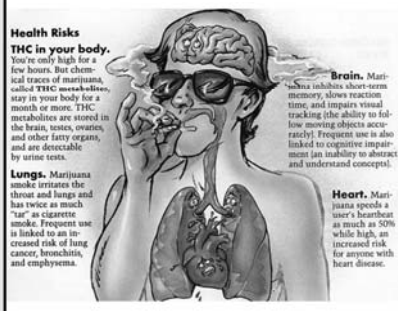
What Do I Tell My Patients?

- Support their attempt to quit
- Encourage FDA approved, evidence-based treatments
- Advise not to use the product indoors or around children
  - Passive exposure to the e-cigarette aerosol
- Ultimate goal is to quit, encourage setting quit date for e-cigarettes
- Inform:
  - Likely not associated with successful quitting, lack of risk reduction with dual use
  - Contain toxic chemicals
  - Possible adverse cardiovascular effects (acute)
  - Lack of evidence on long term risks

Circulation. 2014;129(19):e490-492

Marijuana and the Heart





- Mr Smith, a 48 yo man with heart disease, heart attack at age 45. He smokes marijuana for chronic pain relief. He feels this is safer than using opioids. Which of the following should you tell him?

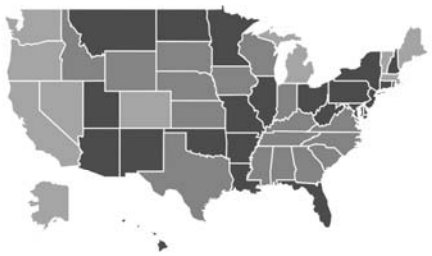
A. Smoking marijuana likely increases his risk for cancer
B. Smoking marijuana decreases heart rate and blood pressure
C. Smoking marijuana decreases frequency of angina
D. Smoking marijuana may increase the likelihood of heart attacks

Cannabis (Marijuana)

- Introduced to US in mid -1800's as medicinal product
- Sanctioned in 1937
- Controlled Substance Act resulted in prohibition in 1970
- California led the way for legalization of marijuana in 1996
- As of November 2018:
  - 33 states and D.C have laws broadly legalizing marijuana in some form. [1]
  - 10 States and D.C have adopted the most expansive laws legalizing marijuana for recreational use
  - Although Louisiana is considered to have legalized marijuana, it cannot be used in a form that can be smoked -- only oils, topical applications and other types

http://www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html

State Marijuana Laws in 2018 Map



used in a form that can be smoked -- only oils, topical applications and other types

http://www.governing.com/gov-data/safety-justice/state-marijuana-laws-map-medical-recreational.html

Information is current as of Nov. 7, 2018.

Cannabis Smoke

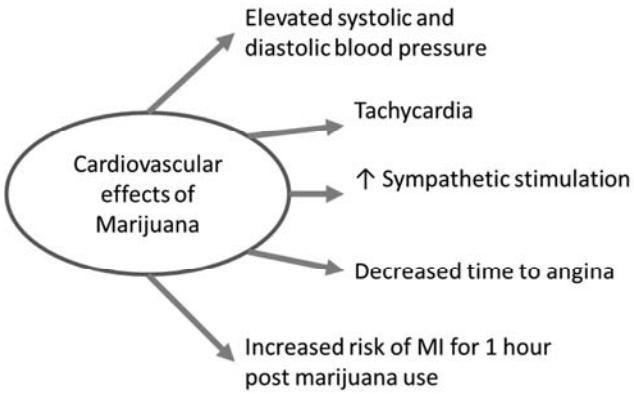
- Contains thousands of organic and inorganic chemical compounds
- Compared with tobacco, smoking marijuana was associated with:
  - Nearly 5-fold greater increase in the blood carboxyhemoglobin level
  - 3-fold increase in the amount of tar inhaled
  - Retention in the respiratory tract of one third more inhaled tar
- Over fifty known carcinogens have been identified in cannabis smoke
- Evidence is quite mixed as to cancer risk

N Engl J Med. 1988;318(6):347-351

Marijuana and the Heart

- Known hemodynamic effects of marijuana (and THC):[1,2,3]
  - Dose-dependent increase in heart rate of 20% to 100%
  - Supine hypertension
  - Postural hypotension common
    - Tolerance develops to the acute effects of marijuana smoking and THC over a few weeks
- Increased in myocardial oxygen demand with a decrease in oxygen supply due in part to carboxyhemoglobin
  - Maximum exercise performance decreases
- Increased levels of serum apoC-III in heavy chronic users[4]
  - Increased triglycerides

1. Circulation. 2001;103:2805-2809
2. *N Engl J Med. 1974;291:65–67*
3. Clin Pharmacol 2002; 42: 64S–70S
4. Molecular Psychiatry (2010) **15,** 101–112



http://www.acc.org/latest-in-cardiology/articles/2016/09/22/08/58/marijuana-and-coronary-heart-disease#sthash.ZoLcQ2mr.dpuf

Marijuana and Cardiovascular Risks

Possible marijuana-induced cardiac effects:[1,2,3,4, 5, 6, 7]

- Frequent premature ventricular beats
- Decreased anginal threshold
- Increased risk of heart attack
- Atrial Fibrillation
- Stroke
- 3-fold risk of dying from HTN, risk increases with each additional year of use
- New Study (young and middle aged) - 26% increase in the risk of stroke and 10 percent increase in developing HF (even after accounting for demographic factors and additional lifestyle risk factors)

1. Am J Cardiol. 2014. 113(1): 187-190
2. Int J Clin Pract 2008. Feb; 62(2): 308-13
3. Clin Pharmacol 2002; 42: 64S–70S
4. Stroke. 2013;44:558-563
5. DOI: https://doi.org/10.1177/2047487317723212
6. ACC News Story March 9, 2017 (https://www.acc.org/about-acc/press-releases/2017/03/09/14/05/marijuana-use-associated-with-increased-risk-of-stroke-heart-failure)
7. Journal of the American College of Cardiology Mar 2018, 24728; DOI: 10.1016/j.jacc.2018.02.047

Marijuana and Risk of Myocardial Infarction

- Risk for developing heart attack 4.8 times higher than average in the hour immediately after marijuana use. Risk declines rapidly after 1 hour[1]
- Several small case reports describe a similar temporal relation
  - The majority of patients studied after marijuana use had either normal coronary arteries or minimal coronary irregularities
- Other large sample size, long-duration, longitudinal studies also failed to show any statistically significant increase in mortality due to cardiovascular events in marijuana users[2]
- However, in patients who already had a heart attack, marijuana use more than once a week was associated with a threefold increase in mortality[3]

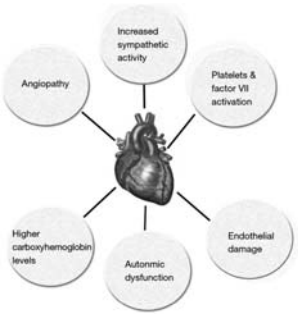
1. Circulation. 2001;103:2805-2809
2. Am J Cardiol 2006;98:478-84
3. Am Heart J 2008;155:465-70.

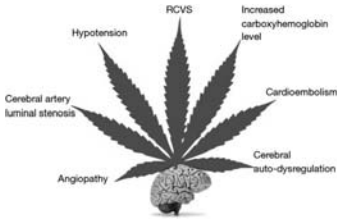
Marijuana and Cardiovascular Risks

- The mechanisms of marijuana-induced cardiac effects are only partially understood:
- Stimulation of the sympathetic nervous system ("fight or flight") and a decrease in the parasympathetic autonomic tone?
- Abnormalities in microcirculation?
- Increased in myocardial oxygen demand with a decrease in oxygen supply due in part to carboxyhemoglobin
- Oxidant gases cause cellular stress and may contribute to cardiovascular risk by activating platelets, promoting formation of oxidized LDL, and inducing an inflammatory response

Am J Cardiol. 2014. 113(1): 187-190

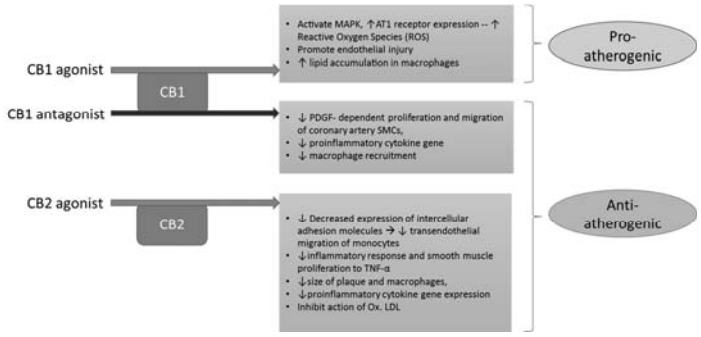
Proposed mechanisms for cannabis-induced cardiovascular and cerebrovascular effects





38 J Thorac Dis. 2017 Jul; 9(7): 2079-2092

Cannabinoid Receptors (CB1 and CB2)



http://www.acc.org/latest-in-cardiology/articles/2016/09/22/08/58/marijuana-and-coronary-heart-disease#sthash.ZoLcQ2mr.dpuf

Marijuana and Atherosclerosis

Despite biological effects, RCT clinical trials have yet to show either an increase or decrease in atherosclerosis with cannabinoids. Looking at the effects of the CB1 receptor antagonist rimonabant on atherosclerosis :

- STRADIVARIUS trial (N=839):
  - Percentage atheroma volume (primary end point) did not change with rimonabant, but total atheroma volume (a secondary end point) decreased[1]
- AUDITOR trial (N=661)
  - No decrease in the progression of carotid artery intima-media thickness[2]

1. JAMA 2008;299:1547-60
2. Heart 2011;97:1143-50

Is the cardiovascular system a therapeutic target for cannabidiol?

In pre-clinical animal studies:

- CBD enhances the vasorelaxant responses in animal models of impaired endothelium-dependent vasorelaxation
- In vivo CBD treatment protects against ischemia-reperfusion damage and against cardiomyopathy associated with diabetes
- CBD has been shown to reduce infarct size and increase blood flow in animal models of stroke
- CBD reduces the cardiovascular response to models of stress, applied either systemically or intracranially
- CBD attenuated myocardial dysfunction, cardiac fibrosis, oxidative stress, inflammation, cell death, and interrelated signaling pathways in mice with diabetic cardiomyopathy

Br J Clin Pharmacol. 2013; Feb;75(2):313-22
Br J Pharmacol. 2010 Jul;160(5):1234-42. doi: 10.1111/j.1476-5381.2010.00755.x.
J Am Coll Cardiol. 2010 Dec 14;56(25):2115-25. doi: 10.1016/j.jacc.2010.07.033

- Recent federal data reported a stunning 455 % increase in marijuana consumption among U.S. adults ages 55-64 years and 333 % in ages over 64 years between 2002 and 2014[1]
- One in eight Americans say they smoke marijuana[2]

1. National Survey on Drug Use and Health, United States, 2002–2014. MMWR Surveill Summ 2016;65 (No. SS-11):1–25. DOI: http://dx.doi.org/10.15585/mmwr.ss6511a1
2. 2. Gallup.com, 19 July 2017, news.gallup.com/poll/214250/say-tried-marijuana.aspx

Is Vaping safer than Smoking?

- Cannabis was vaporized at three different temperatures (338°F, 392°F, and 446°F), with the cannabinoid-to-byproduct ratio measured using high-performance liquid chromatography (HPLC)[1]
- The gas phase of the vapor consists mainly of cannabinoids, with trace amounts of other noxious byproducts
- In contrast, over 111 compounds were identified in the combusted smoke
- Fewer harmful byproducts in vaping versus smoking, but also temperature matters, showing less harmful toxins when vaporizing at lower temperatures
- There is a 56% reduction in tars and a qualitative reduction in carbon monoxide in vaporizer versus smoking[2]

1. Journal of Cannabis Therapeutics, Vol. 4(1), 2004
2. Journal of Pharmaceutical Sciences. Vol 95(6), June 2006

Challenges with Current Studies

- Most evidence to date comes from case studies or small cohort studies, with poor- or moderate-quality data, inadequate assessment of marijuana exposure and minimal exposure in the populations studied, and variation in study design
- No RCT yet looking at long term cardiovascular effects
  - Still Schedule 1 drug: "no currently accepted medical use and a high potential for abuse"
- Increased use of both recreational and medical marijuana currently will hopefully prompt more research regarding the safety of marijuana use

Ann Intern Med. 2018;168(3):187-194

Marijuana: What We Know

- Almost all the studies here involve smoked cannabis. We know little to nothing about edibles and other means of administration
- Marijuana causes 1) tachycardia 2) decreased exercise time to angina 3) increases the risk of triggering acute coronary syndrome
- Marijuana use can precipitate an acute event in susceptible patients and may be associated with increased mortality in patients with history of heart attack
- There are no clinical data to suggest any definite relationship between recreational marijuana use and atherosclerosis (studies ongoing, more needed)
- Long-term, large sample size studies have failed to show an increase in cardiovascular mortality related to marijuana use

What Do I Tell My Patients?

- Remember to ASK:
  - A history of marijuana use often not sought by providers, and often patient's response not always truthful
- Patients should be aware of the potential adverse effects of marijuana: tachycardia, decreased anginal threshold, increased risk of triggering an heart attack, stroke
- Marijuana use can precipitate an acute event in susceptible patients and may be associated with increased mortality in patients with previous history of heart attack, HTN
- Modality probably matters: Smoke, vape, eat, tincture, topical

Am J Cardiol. 2014. 113(1): 187-190
http://www.acc.org/latest-in-cardiology/articles/2016/09/22/08/58/marijuana-and-coronary-heart-disease

Ms Smith, a 52 yo woman with diabetes, hypertension comes to see you for follow up. She started using e-cigarettes to quit smoking and has decreased her tobacco use from 1 ppd to 1/4 ppd. Which of the following is true?

A. E-cigarettes have no known adverse cardiovascular effects
B. E-cigarettes contain same amount of toxins as conventional cigarettes
C. E-cigarettes are safe to use indefinitely if it keeps her from smoking
D. E-cigarettes are likely not as effective as other FDA approved medications for smoking cessation

- Mr Smith, a 48 yo man with heart disease, heart attack at age 45. He smokes marijuana for chronic pain relief. He feels this is safer than using opioids. Which of the following should you tell him?

A. Smoking marijuana likely increases his risk for cancer
B. Smoking marijuana decreases heart rate and blood pressure
C. Smoking marijuana decreases frequency of angina
D. Smoking marijuana may increase the likelihood of heart attacks

Thank You!

HIV Risk Reduction

PreExposure Prophylaxis (PrEP) and Non-Occupational Post Exposure Prophylaxis (nPEP)

DATE: FEBRUARY 14, 2019 PRESENTED BY: ANTHONY CHENG, M.D.

Some Slides courtesy of Oregon AETC, Melissa Murphy MD, Joanne Stekler, MD MPH, Chris Evans M, and John Nusser MD MS

Disclosures

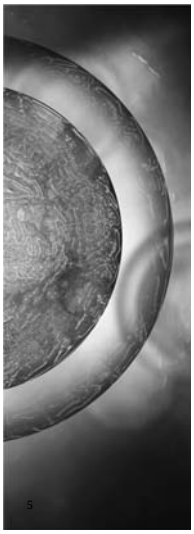
- No Conflicts of Interest or Relationships to disclose.

Objectives

- Describe and counsel on the risks/benefits of PrEP
- Determine who should be offered PrEP
- Oversee required PrEP care plan monitoring.
- Determine eligibility and presscribe nPEP using appropriate resources

Outline

- What is PrEP?
- Why Prescribe PrEP?
- Efficacy and adherence
- Eligibility criteria
- Prescribing and Monitoring
- Introduction to nPEP



Case 1

A 27 year old previously healthy man presents to an urgent care center with fever, sore throat, lymphadenopathy, severe fatigue and a diffuse erythematous rash. His symptoms have been present for approximately 48 hours and his history reveals unprotected receptive anal intercourse with another man 12 days prior to the onset of his symptoms. He had a negative HIV antibody test approximately 6 months ago. His physical examination shows a temperature of 39.0 C, lack of exudative pharyngitis, the presence of cervical and axillary lymphadenopathy, and a generalized morbilliform rash. All laboratory tests are pending.

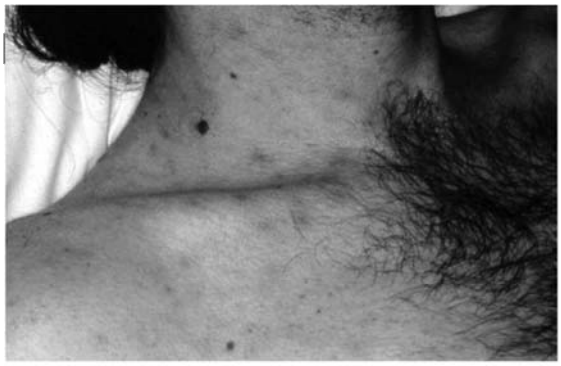


Figure 1 – Morbilliform Rash
This patient presented with a macular rash most prominent on the neck, chest, back, and abdominal region. The numerous lesions were flat, erythematous, and non-blanching.

Primary HIV Infection

- Symptomatic in many newly infected individuals
- Symptoms occur 2-6 weeks after exposure to HIV
- Median duration of symptoms 15-28 days

TABLE 5. Expected frequency of associated signs and symptoms among persons with signs and symptoms of acute retroviral syndrome

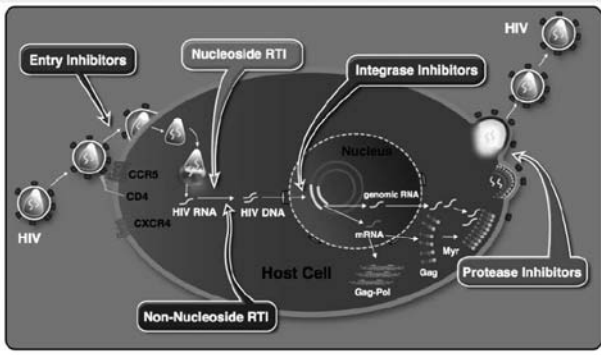
Symptom/sign	%
Fever	96
Lymphadenopathy	74
Pharyngitis	70
Rash Erythematous maculopapular with lesions on face, trunk and sometimes extremities, including palms and soles; mucocutaneous ulceration involving mouth, esophagus or genitals	70
Myalgia or arthralgia	54
Diarrhea	32
Headache	32
Nausea and vomiting	27
Hepatosplenomegaly	14
Weight loss	13
Thrush	12
Neurologic symptoms Meningoencephalitis or aseptic meningitis; peripheral neuropathy or radiculopathy; facial palsy; Guillain-Barré syndrome; brachial neuritis; or cognitive impairment or psychosis	12

MMWR Recommendations and Reports, January 21, 2005 / 54(02):1-20

What is PrEP?

- A prevention strategy in which individuals at **highest risk** of HIV infection take a medication **regularly** (along with continued behavioral **risk-reduction** strategies) to prevent HIV infection.
- Tenofovir/emtricitamine (TDF/FTC) or Truvada

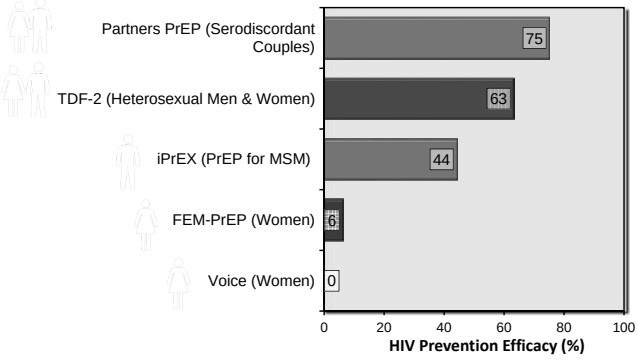
HIV Drug Targets



2 nucleoside analog reverse transcriptase inhibitors
- Tenofovir (TDF): adenosine analog
- Emtricitabine (FTC): cytosine analog

Estimated Protection from PrEP All Participants

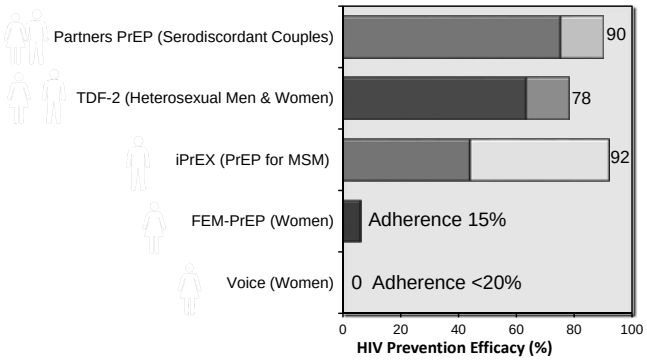
- Estimated Protection from PrEP



Source: Marrazzo JM et al. JAMA. 2014;312:390-409.

Estimated Protection from PrEP

All participants (Dark bar) vs Adherent Participants (Light bar)



Source: Marrazzo JM et al. JAMA. 2014;312:390-409.

At Risk Populations

- 40,000 new cases of HIV in the US in 2014
- At risk population: 1.2 million

Population	Number at risk	Percent of population at risk	Efficacy of PrEP (ideal)
MSM	492,000	25% (1 in 4)	92%
IDU	115,000	20% (1 in 5)	73.5%
Heterosexual	624,000	0.4% (1 in 200)	90%

PrEP reduces HIV infection in high risk MSM groups with efficacy up to 92%.

Efficacy is directly related to adherence.

USPSTF Recommendations 2018 Draft

- The USPSTF recommends that clinicians offer pre-exposure prophylaxis (PrEP) with effective antiretroviral therapy therapy to persons who are at risk of HIV acquisition.

CDC Guidelines for PrEP: 2014

Daily oral PrEP with the fixed-dose combination of tenofovir disoproxil fumarate (TDF) 300 mg and emtricitabine (FTC) 200 mg has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults; therefore,

- PrEP is recommended as one prevention option for sexually-active adult MSM (men who have sex with men) at substantial risk of HIV acquisition. **(IA)**
- PrEP is recommended as one prevention option for adult heterosexual men and women who are at substantial risk of HIV acquisition. **(IA)**
- PrEP is recommended as one prevention option for adult injection drug users (IDU) at substantial risk of HIV acquisition. **(IA)**

https://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf

Heterosexually Active Men & Women

- Adult
- Sexually active in prior 6 months
- No acute or established HIV infection
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual; also evaluate by MSM criteria)
- Infrequently uses condoms during sex with 1 or more patterns of unknown HIV status who are known to be at substantial risk of HIV infection (IDU or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner

Indications for PrEP use by MSM

- Adult man, without acute or established HIV infection
- Any male sex partners in the past 6 months
- Not in a monogamous partnership with a recently tested, HIV-negative man

AND at least one of the following

- Any anal sex without condoms (receptive or insertive) in the past 6 months
- Any STI diagnosed or reported in the past 6 months
- Is in an ongoing sexual relationship with an HIV-positive male partner

Indications for PrEP use by People who Inject Drugs

- Adult person, without acute or established HIV infection
- Any injection of drugs not prescribed by a clinician in the past 6 months

AND at least one of the following

- Any sharing of injection or drug preparation equipment in the past 6 months
- Been in a methadone, buprenorphine or suboxone treatment program in the past 6 months
- Risk of sexual acquisition (assess for sexual transmission criteria)

Who should be offered PrEP?

Consider offering PrEP to HIV-negative adults 18 and over who in the last six months have had one or more of the following:

- Any sex partner with HIV or HIV risk factors (IDU or MSM)
- Condomless vaginal or anal sex with a partner of unknown HIV status who is known to be at substantial risk of HIV infection
- A bacterial sexually transmitted infection (gonorrhea/chlamydia/syphilis)
- Injected drugs and shared needles/equipment
- Used non-occupational post-exposure prophylaxis (nPEP = taking antiretrovirals within 72 hours of a recent exposure to prevent becoming infected with HIV)
- Survival/transactional sex
- Participated in a drug treatment program
- Interest in trying to conceive with a partner who is HIV-positive

Men or transgender persons engaging in receptive anal sex benefit the most from PrEP.

Contraindications

- HIV Positive
- eCR/Cl < 60 ml/min
- Possible recent HIV exposure
  - If patient presents within 72 hours of possible HIV exposure, offer **nPEP**, then consider PrEP

If you have questions about PEP, call the helpline:
Clinician Consultation Center PEPline
http://nccc.ucsf.edu/clinician-consultation
1-888-448-4911

Caution

- Hepatitis B (HBV) infection: Can flare up when stopping the medications used for PrEP; check the Hepatitis B Surface Antibody/Antigen (HBsAb/Ag) prior to initiation of PrEP
- Prolonged Flu-like illness: Consider evaluation for acute HIV infection with HIV RNA PCR before initiation of PrEP
- In patients with conditions such as diabetes mellitus or hypertension, there may be an increased risk of kidney disease; consider more frequent creatinine monitoring
- Difficulty with adherence
- Pregnancy or breastfeeding
- Osteoporosis
- Adolescents

Who would **NOT** be a good candidate for PrEP?

A. Someone who engages in condomless vaginal or anal sex with a partner of unknown HIV status who is known to be at substantial risk of HIV infection.

B. Someone who is HIV positive.

C. Someone who has a creatinine clearance of 65 ml/min.

D. Someone who injects drugs and shares needles or equipment.

Side Effects

- Nausea and headache: 10% of patients, usually resolve within 1 month.
- Renal Dysfunction: small risk, typically reversible if PrEP is discontinued.
- Bone mineral density decrease: PrEP associated with 1% decrease; no increased risk of fractures

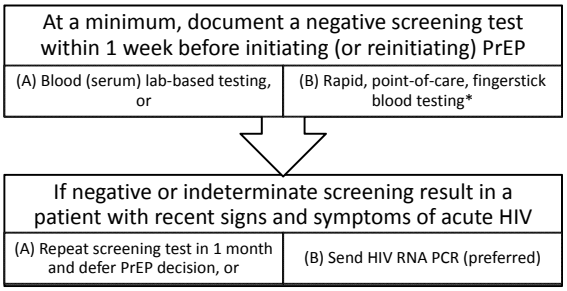
Counseling

- When taken daily with excellent adherence, PrEP is over 90% effective for preventing HIV
- Maximum drug levels:
  - Rectal tissues: 7 days
  - Blood: 7 days
  - Vaginal tissues: 20 days
- Continue PrEP for 28 days after last potential HIV exposure
- PrEP does not prevent gonorrhea, chlamydia, syphilis, genital warts, or hepatitis C

Counseling

- Reproductive goals and contraception
- Symptoms of acute HIV infection
- Risks of stopping and restarting PrEP, need to notify provider
- Insurance and medication assistance
- Refill policies and procedures

HIV Screening Prior to Initiation



Source: US Public Health Service. Clinical practice guidelines for PrEP. May 2014.

First Prescription

Every visit:
Assess adherence
Risk reduction counseling
Provide condoms

Week 1
- Call: prescription filled? Adherence? Side effects?

Month 1 (optional)
- Consider HIV test (ideally 4th generation HIV ag/ab)
- Assess adherence and side effects.
- After confirmation of ongoing eligibility:
  - Prescribe no more than 90-day supply of PrEP
    - Truvada 1 tablet PO daily *(tenofovir 300mg + emtricitabine 200mg)*
    - Vaccination of Hepatitis A and B especially in MSM if non-immune
  - Many prescribers will see pt in 1 month

http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf

Follow-up:

Every visit:
Assess adherence
Risk reduction counseling
Provide condoms

- At least every 3 months:
  - HIV test (ideally 4th generation HIV ag/ab)
  - Pregnancy test
  - Assess adherence
  - Evaluate need for PrEP (sexual history)
  - Provide 3 month refill

CDC. MMWR Morb Mortal Wkly Rep. 2011;60:65-68. Tenofovir/emtricitabine [package insert]. 2012.

Follow-up:

Every visit:
Assess adherence
Risk reduction counseling
Provide condoms

- At least every 6 months:
  - Gonorrhea/chlamydia and syphilis (more frequently depending on risk)
- Renal Function
  - Creatinine at baseline
  - Creatinine at 3 months then every 6 months (more frequently if patient has renal risk factors)
- At every visit
  - Risk reduction counseling
  - Assess for signs/symptoms of acute HIV infection.

CDC. MMWR Morb Mortal Wkly Rep. 2011;60:65-68. Tenofovir/emtricitabine [package insert]. 2012.

Discontinuation

Every visit:
Assess adherence
Risk reduction counseling
Provide condoms

- If patient acquired HIV
  - Do resistance testing
  - Establish linkage to HIV care
- If person has chronic hepatitis B infection
  - Check liver function tests (case reports of hepatitis flares after discontinuing PrEP)

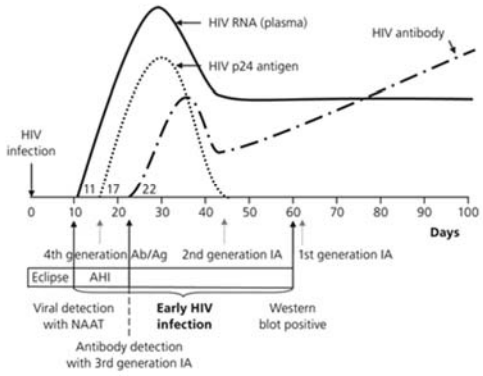
http://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf

Summary of Recommended Laboratory Evaluation

Test	Baseline	Every 3 months	At least every 6 months	Notes
HIV screening assay	✓	✓		Consider need for HIV RNA PCR
HBV antibody panel And HCV antibody	✓			Offer HBV Vaccination if not immune
Serum creatinine	✓		✓	Avoid PrEP if CrCl<60mL/min
General STI screen	✓		✓	Include oral/rectal Screen for MSM if risk
Pregnancy test for women	✓	✓		

Source: US Public Health Service. Clinical practice guidelines for PrEP. May 2014.

HIV Tests



HIV Testing Pearls

- Use the 4th generation test, which is more sensitive to acute infection.
  - Combined HIV antibody test and p24 antigen
- Viral Load if you suspect acute HIV
- Viral Load in 2 weeks if very recent exposure

- US PHS. Clinical guidelines for PrEP. May 2014
- Branson, B. HIV diagnosis / new tests, new algorithms CROI 2012, Seattle, WA. Abstract #114
- Daskalakis D. Topics in Antiviral Medicine Feb/March 2011:18-22

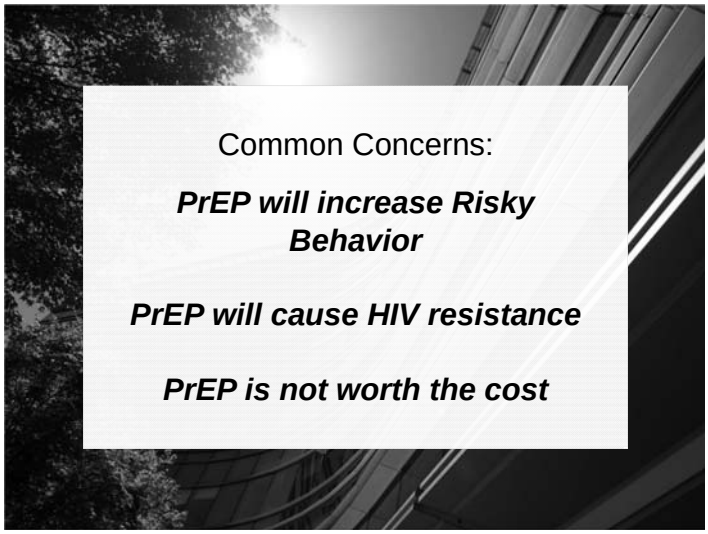
CASE 2

Patient: 34 year old male

- Reason for visit: Yearly check-up, no complaints this visit.
- Medical History: Prior history of Chlamydia 4 years ago. Otherwise, no other medical conditions.
- Physical Exam: Unremarkable
- Social History: Works as a bank teller. He has been in a relationship with his male partner for the past 5 years.

Behavioral Risk-Reduction Counseling

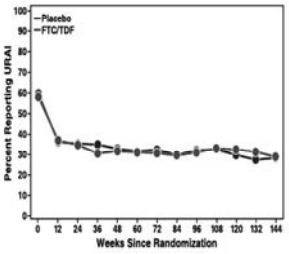
1. Elicit barriers and facilitators to:
   - Consistent condom use
   - Reducing substance use
2. Support risk-reduction efforts
3. Monitor behavioral adherence in a non-judgmental manner



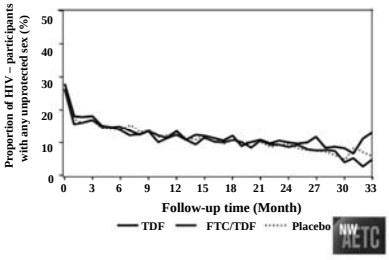
Risky Behavior and PrEP

- Condomless sex was LESS common over time in iPrEx and Partners PrEP.
- Subjects did not know if they were on PrEP or placebo.

iPrEx



Partners PrEP



What is the risk of drug resistance to Truvada if a person acquires HIV while on PrEP?

Number of HIV Seroconverters on *Active PrEP Arms* With HIV Resistance*		
Trial	**N**	HIV Infected After Enrollment, Resistant / Seroconverters (randomized to active drug)
iPrEX[4, 5]	1224	0/36
Partners PrEP[6, 7]	3140	4/51
TDF2[8]	601	0/10
FEM-PrEP[9, 10]	1024	4/33
VOICE[11]	1978	1/113
TOTAL	7967	9/243 (3.7%)
Modified Total (After exclusion of resistance)	**7967**	**5/243 (2.0%) or 0.06% of exposed**

*For 454 sequencing, resistance levels >1% of variants likely to be transmitted

Is PrEP Worth the Cost?

- PrEP Costs about **$24,000 per year.**
- Preventing one new HIV infection will save the healthcare system an estimated **$379,668** (in 2010 dollars) in lifetime HIV care costs.
- The total lifetime treatment cost for Oregon patients diagnosed with HIV in 2009 (235 patients) is **$86 million.**

https://www.cdc.gov/hiv/programresources/guidance/costeffectiveness/index.html

Paying for PrEP

- Since brand-name Truvada was approved for HIV prevention six years ago, its average wholesale price has increased by about 45 percent.
- All Medicaid Plans in Oregon and most health insurances cover Truvada for PrEP (patient just pays co-pay for doctor's visit, and lab tests and drug co-pay/deductible*)
- Insurance may require prior authorization
- Resources at end of this presentation to help patient pay for PrEP, including contact to PrEP Navigators.
- Remember, there are varying degrees of benefit for all prescription

https://www.npr.org/sections/health-shots/2018/06/30/624045995/rising-cost-of-prep-a-pill-that-prevents-hiv-pushes-it-out-of-reach-for-many

Non-Occupational Post Exposure Prophylaxis (nPEP)

72 hours

- First dose AS SOON AS POSSIBLE or within 72 hours of possible HIV exposure
  - Offer nPEP
  - Then consider PrEP

Truvada® tenofovir disoproxil fumarate (tenofovir DF or TDF) (300 mg) with emtricitabine (200 mg) once daily	PLUS	**Isentress®** raltegravir (RAL) 400 mg twice daily
		OR
		Tivicay® dolutegravir (DTG) 50 mg daily

Addendum to HIV Prophylaxis for Adults after Sexual Assault: Recommendations for Healthcare Providers, Oregon Health Authority October 14, 2016.

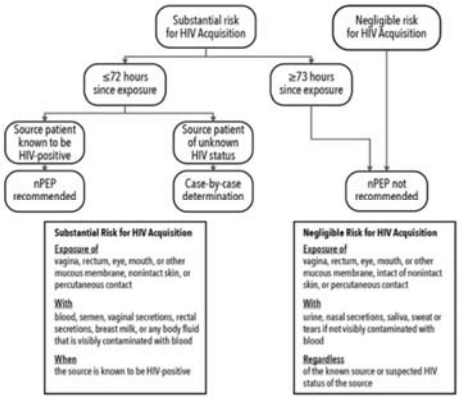
History of Present Illness

- Exposure:
  - Date and time
  - Type of exposure
- Source
  - HIV (VL, CD4, HAART use, resistance), Hep B, Hep C status
- Patient
  - HIV (frequency and timing of most recent testing)
  - Hep A, Hep B, Hep C, vaccination history.
  - PMH, Meds (including PrEP, adherence)
  - Pregnancy, contraception, breastfeeding
  - Acute HIV symptoms

Labs

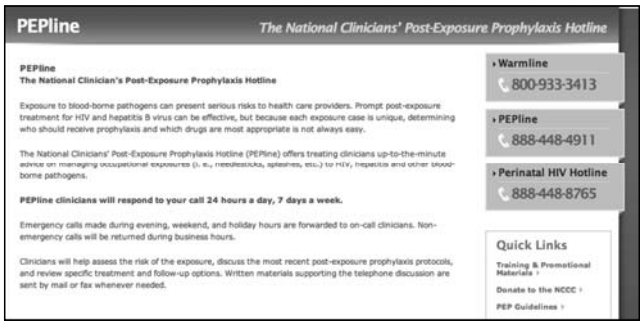
- HIV – 4th generation test
- ALT, AST, Cr
- Hep C ab, Hep B serology
- Pregnancy test
- Syphilis serology

Algorithm for evaluation and treatment of possible non-occupational HIV exposures



Patient Education

- Use condoms, abstain from sex until HIV transmission ruled out (negative HIV test 3 months after possible exposure or source person found to be HIV negative).
- Side effects: nausea, GI upset, headache, myalgias. Consider rx anti-emetic
- Support adherence
- Reinforce need for follow-up within 24-72 hours of initial visit, 4-6 weeks, 3 months.



Post-Exposure Prophylaxis Line (PEPline)
888-HIV-4911

Resources

- US Public Health Service. (2014) "Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline." Retrieved fromhttps://www.cdc.gov/hiv/pdf/guidelines/PrEPguidelines2014.pdf
- Center for Disease Control and Prevention. (2017, August 31). "Pre-Exposure Prophylaxis (PrEP)" Retrieved from https://www.cdc.gov/hiv/risk/prep/index.html
  - Resources for providers and patients
- PrEP Warmline 1-855-HIV-PREP
- PEP Line 1-888-HIV-4911
- Free preceptorship / CME through AETC 1-206-543-2704

Thank You

An Early Psychosis Update Through One Individual's Journey…

Craigan Usher, MD
Oregon Health & Science University

Oregon Early Assessment & Support Alliance
wellness focused

"Drugs don't cure schizophrenia and they usually don't work for a person with a mental health disorder if that person doesn't have a place to live and an adequate support system. Psychiatry places a bad bet for itself and its patients if it expects quick biological breakthroughs and tamely accepts a restricted role as pill prescriber."

-Allen Frances, MD

Frances, A. Resuscitating the biopsychosocial model. Lancet Psychiatry. 2014 Dec;1(7):496-7.

Disclosures / Conflicts of Interest

- I receive salary support from the Oregon Health Authority/the Early Assessment & Support Alliance Center for Excellence – OHSU/PSU School of Public Health
- Previously received grant funding from private donors for Meals, Mindfulness & Moving Forward: A Multi-modal Lifestyle Intervention project for youth with early psychosis
- I will discuss non-FDA approved pharmacological treatments

5 Learning Objectives

① Identify common symptoms of emerging psychosis/schizophrenia spectrum disorders

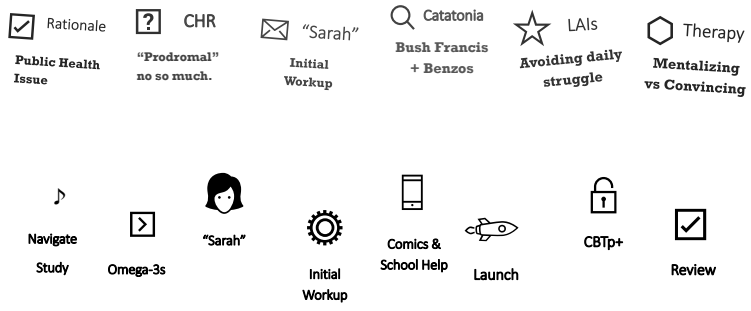
② List three "go to" or first-line agents to address the symptoms of psychosis

③ Describe two advantages and two disadvantages of utilizing long-acting injectable (LAI) medications

④ Utilize materials from this grand rounds for psychoeducation with families

⑤ List principles of emerging cognitive behavioral therapy for psychosis (CBTp) to help young people, transition age youth, and adults who are impacted by psychosis

Grand Rounds Plan



What's at stake?

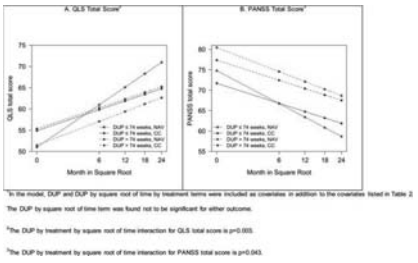
- According to a recent study, in the year following first-episode psychosis, insured individuals age 16-30…
  - were 24x more likely to die than the general population of same-age people, and 89x the general population
  - 41% did not receive any psychotherapy
  - 61% did not fill any antipsychotic medication prescriptions

Schoenbaum M, Sutherland JM, Chappel A, et al. Twelve-month health care use and mortality in commercially insured young people with incident psychosis in the United States. Schizophr Bull. 2017; doi:10.1093/schbul/sbx009

- In one study, across 34 clinics in 21 states where ⅓ utilized specialized multidisciplinary treatment (NAVIGATE) and ⅓ TAU, outcomes were better for the NAVIGATE group.
- The NAVIGATE group had:
  - More improvement in symptoms and quality of life
  - Remained in treatment longer
  - Improved work and school participation
- Particularly for those with a duration of untreated psychosis (DUP) <74 weeks.

Kane JM, Robertson DG, Schooler NR et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program [published online ahead of print October 20, 2015]. Am J Psychiatry. appi.ajp.2015.15050632.

DUP <74 weeks is optimal



Kane JM, Robertson DG, Schooler NR et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program [published online ahead of print October 20, 2015]. Am J Psychiatry. appi.ajp.2015.15050632.

Clinical High Risk (CHR)

- Attenuated psychotics symptoms
- Social, emotional, and cognitive functioning deficits
- Seeking help for these problems
- Approximately a 20% risk of conversion to psychosis within two years
- Note: about 75% of people who develop schizophrenia have a "prodomal" phase

Fusar-Poli P, Cappucciati M, Borgwardt S et al. Heterogeneity of psychosis risk within individuals at clinical high risk. JAMA Psychiatry 2016;73:113-20.

Tools for Assessing Psychosis Risk

- OUTPATIENT & SCHOOL SCREENING TOOL
  - PQ16 (Prodromal Questionnaire 16) -- https://www.mcpap.com/pdf/PQ-16.pdf
  - Cut off 6
- Instrument for the retrospective assessment of onset of schizophrenia – Hafner et al,1992
- Bonn Scale for the assessment of basic symptoms -- Huber *et al*, 1980
- Structured Interview for Prodromal Symptoms or SIPS -- McGlashan/Walsh, 1996
- Scale for prodromal symptoms (SOPS) –McGlashan, 1996
- Multidimensional assessment of psychotic prodrome -- Yung and McGory,1996
- Comprehensive assessment of At-Risk Mental States (CAARMS) -- McGory *et al*, 2003

Interventions that have been studied… PUFAs

Omega-3 FA ☺

- 81 research subjects ages 13-25
  - 41 individuals treated with 1.2g/d of Omega-3 Fatty Acid Treatment
    - containing 700 mg of eicosapentaenoic acid (EPA), 500 mg of docosahexaenoic acid (DHA), and 10 mg of Vitamin E.
  - 40 administered "fishy" smelling placebo
  - 12 weeks of treatment with 12month follow-up
  - 2/41 O3FA transitioned to psychosis vs 11/40 (p=.004)
  - Also reduced positive symptoms, negative symptoms, and global symptoms, improved functioning compared to placebo

Amminger, GP, Schafer, MR, Papgeorgiou, K, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2010. 67(2):146-54.

Interventions that have been studied… PUFAs

Omega-3 FA ☺

On follow-up 7 years later…

88% participated in interviews or consented to review of hospital records

Psychosis:

10% of Omega-3 FA group converted to psychosis

40% of Placebo group converted to psychosis

Medication Treatment

29% of Omega-3 FA group had received antipsychotic medication

54% of Placebo Control group received an antipsychotic

Amminger GP, Schafer MR, Schlogelhofer M, et al. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. Nat Commun. 2015;6:7934

Interventions that have been studied… PUFAs

Omega-3 FA ☹

Larger study by McGorry and colleagues showed that in 304 adults at UHR for psychosis receiving CBT + placebo vs CBT + ω-3FA; at 12mos:

- ω-3 group had 11.5% conversion
- Placebo group had 11.1% conversion

Take homes:

- Study featured lower rate of conversion than one would expect
- ω-3 and/or CBT may work

McGorry PD, Nelson B, Markulev C, et al. Effect of ω-3 polyunsaturated fatty acids in young people at ultrahigh risk for psychotic disorders. JAMA Psychiatry. 2017:1(74):19-27.

CHR: Interventions that have been studied…

Recent meta-analysis (2,035 patients) showed no difference in rates of transition to psychosis for:

- Needs-based Interventions +
- CBT
- Family Therapy
- ω-3 FA
- D-Serine
- Aripiprazole
- Olanzapine
- Risperidone
- Ziprasidone

Davies C, Cipriani A, Ioannadis JPA, et al. Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. World Psychiatry; 2018;17(2):196-209.

CHR

Take Homes…

- Questioned some of the "pooling together" methods
- Adaptive Interventions which change based on:
  - Psychological Features
  - Patient Preference
  - Mechanism-linked Biomarkers
  - Adjusted over time…
- The advantage:
  - delivering treatment to those who need it the most
  - intensifying potentially helpful tx
  - halting potentially nonhelpful or deleterious interventions
  - Avoiding the "one size fits all" trap

Nelson B, Amminger GP, McGorry PD. Recent meta-analyses in the clinical high risk for psychosis population: clinical interpretation of findings and suggestions for future research. Frontiers Psychiatry, 2018;doi: 10.3389/psyt.2018.00502

The Case of "Sarah"

Details changed to protect individual's identity

"Sarah"

- 13 year-old 7th grader who lives with parents from a rural town
- Referral from PCP:
  - A's and B's in school
  - "Marches to the beat of her own drum"
  - History of generalized anxiety disorder
  - For the past six months has been
    - Unable to focus
    - Failed to eat/drink regularly
    - Been moving incessantly alternating with times of being
    - Frozen
  - Episodes of freezing led to EEGs x 2 (both normal)
  - Intermittent quality led many to believe she is "faking"

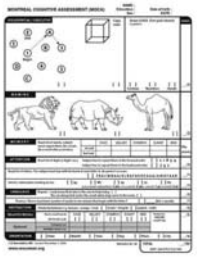
In waiting area…

- Nystagmus (4-5 beats up and to the left)
- Blank stare
- Non-purposeful drawing on magazine
- Very flat midface
- Incessant drumming of hands
- Ataxic featuring arms and trunk swaing back-and-forth, side-to-side

Bush-Francis Catatonia Rating Scale

- Total score of 22
- Symptoms of excitement → drumming
- Intermittent immobility →staring for hours
- Grimacing/Vocal changes →"sounding possessed"
- Intermittent mutism→ nonresponsive
- Staring→little blinking, sitting for long stretches
- Mundane posturing→standing for long periods
- Stereotypies and mannerisms→writhing, wriggling, dancing, drumming
- Negativism→seeming obstreperous
- Withdrawal→failing to eat, sometimes for days (30lbs in six months, dropped 25 percentile points on growth curve
- Impulsivity→wandering out of house, school, oblivious that this was problematic

MOCA



- Montreal Cognitive Assessment
  - 8 out of 30
  - Requiring 45min to complete
  - Patient's posture would freeze, mind drift

Review of Sarah's Risk Factors & Symptoms

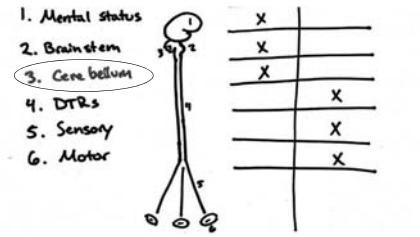
Schizophrenia Symptoms = DHS BeNs

- **Delusions:** None
- **Hallucinations:** None
- **Disorganized Speech:** Yes
- **Behavior** that is grossly disorganized or catatonic: Yes
- **Negative Symptoms**: Yes

Risk Factors

- Some neurodevelopmental abnormality – inviting to few birthday parties since kindergarten
- Advanced paternal age
- Immigrated when very young
- Neighborhood violence
- Witnessed domestic violence
- **No** family history of schizophrenia/psychosis
- **No** attenuated psychotic symptoms when young (harassing imaginary friends)
- **No** history of brief psychotic bouts
- **No** drug use (THC+trauma may increase risk)

Neuro Exam



https://scopeblog.stanford.edu/2017/12/06/how-to-master-the-neuro-exam/

Decision to Medically Hospitalize

- Gait instability/ataxia on neurological examination
- Remarkable MSE
- Marked weight loss
- Younger age
- Lack of availability for testing in patient's community
- Opportunity for video-EEG monitoring
- Consider neuroimaging, basic autoimmune encephalopathy work-up, eating disorder protocol, and finally treatment with benzodiazepines

Autoimmune Workup

MRI w/ contrast & Sleep-deprived EEG and consider…

Blood	CSF	Urine
-ACE -Ammonia -ANA -Anti Sm, Ro, La Ab -Antithyroid Ab -Autoimmune Encephalopathy Panel -BHcg -Drug Screen -C3,C4 -CBC -Ceruloplasm -CMP -CRP -ESR -Lactic Acid -Serum Immunoglobulins -Thyroid Profile -VonWillebrand factor antigen	-Opening Pressure -Cell count -Glucose -Protein -ACE -Autoimmune encephalopathy ab panel -Oligoclonal bands/IgG index	-24 Urine Copper -Porphyrins -Urine Drug Screen

Hospital Course

- MRI with contrast: normal
- Sleep-deprived EEG and 24hr EEG: generalized slowing
- LP: Mayo Clinic Autoimmune Panel including anti-NMDAr Ab all negative
- Urine: Copper normal; negative Tox screen
- CBC, CMP, TSH, Free T4: normal
- Vit D: Low
- EKG: sinus bradycardia improving with weight restoration
- BFCRS: improved to 3
- MOCA: improved to 28/30

Discharge Outpatient Plan

- Primary Care Follow-up with instructions:
  - Re-refer if emerging psychosis
  - Start aripiprazole if emerging + symptoms of psychosis
  - Start lorazepam if emerging catatonia
  - Start Omega-3 FA
- Follow-up with Dietitician
- Supportive Psychotherapy
- Genetics Follow-up: r/o VCFS
- Follow-up with Occupational Therapist
  - Improve executive function: planning, sequencing, carrying out, checking off on checklist various routine tasks

Consulted Colleagues

"Dr. Mufson often shared with us that to be catatonic is to be scared stiff…He also reminded us that though the leading diagnosis/disorder we think of being associated with catatonia is bipolar disorder, schizophrenia may be a more common cause, but one we just no longer see so often because of treatment."

-Todd Eisenberg, MD

Follow-up Appointment #2

- Patient appeared distressed
- Unable to sustain eye contact, eyes darting to computer camera, eyes darting from side to side—clearly paranoid
- Schneiderian first-rank symptoms
  - Thought withdrawal
  - Thought insertion
  - Thought broadcasting
  - Made action
  - Made affect
  - Delusional perception / referential thinking: special meaning to song lyrics as predicting the future or sending special messages – "of course, you know what that means."
- Had grown suddenly violent

Emergency Department

Course of Treatment

ED COURSE…

Medication Treatment

- Metabolically favorable SGAs typically turned to first: Aripiprazole, Lurasidone, Quetiapine
- For this patient, even history of catatonic symptoms, strove for low D2 affinity antipsychotics (quetiapine, olanzapine) OR partial agonist/antagonist (aripiprazole) + benzodiazepine (lorazepam)

Beach SR, Gomez-Bernal F, Huffman JC, Fricchione GL. Alternative treatment strategies for catatonia: A systematic review. Gen Hosp Psychiatry, 2017;48:1-19

ED COURSE…

Medication Treatment

"I don't know what you gave her, but that was a 180 degree turnaround. That was amazing!"

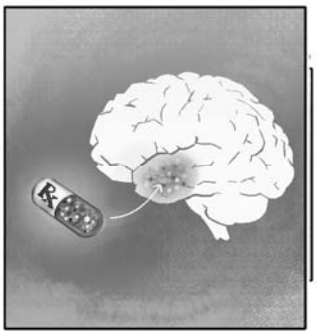
Beach SR, Gomez-Bernal F, Huffman JC, Fricchione GL. Alternative treatment strategies for catatonia: A systematic review. Gen Hosp Psychiatry, 2017;48:1-19

ED COURSE…

Supportive Psychotherapy

- Encourage patient to talk about feelings
- Help the patient tell the story of the current situation
- Learn about patient's strengths and ways they have handled stress in the past – Rocked out a little!
- Highlight strengths and accomplishments
- Learn about key relationships and role play
- Talk about next steps

Cabaniss D. 3-step Supportive Psychotherapy manual for CL/ER/Inpatient Rotations For supervisors and supervisees



Psychoeducation using EASArt Comics

- "During puberty we know that there is a reshaping of connections in the brain. Like someone might trim the limbs of a tree to shape it, the body uses our own immune system to cut some of the extra branches between brain systems in order to make it more efficient. For some reason, though, that process can become hyperactive—particularly in this region called the dorsolateral prefrontal cortex (the side and back of the frontal lobes). It trims too much of the brain's gray matter. This leads to people's thoughts becoming less efficient; they become more confused, less able to make plans and carry them out. The emotional part of the brain then starts to take over. This region, called the ventral tegmental area starts to mark everything we see, hear, feel as vitally important, often frightening…We use medications to try and turn the volume down on this part of the brain which tells us to be scared."

www.easacommunity.org/easa-art.php

Inpatient Treatment Course

- Aripiprazole titrated up and—AIMS and Barnes Akathisia scales being 0—patient consented, moved to aripiprazole long-acting injection.
- Supportive psychotherapy and CBTp informed treatment provided
- Basic psychoeducational assessment completed
- Family meetings to identify and help manage trauma over past few months completed and to outline how best to introduce idea of early psychosis to family

Long-acting Injectables (LAIs): why

- Study 1 (Subotnik et al):
  - 12mos
  - 86 people with first-episode psychosis (FEP)
  - Oral vs LAI risperidone
  - Relapse and/or Exacerbation Rates:
    - 33% for PO group
    - 5% for LAI/IM group
- Study 2 (Schreiner et al):
  - Up to 24mos
  - 382 people with early psychosis (1-5yrs)
  - Oral meds (aripiprazole, haloperidol, olanzapine, quetiapine, paliperidone ER, risperidone) v LAI paliperidone
  - Relapse
    - 20% for PO group
    - 14.8% for LAI group

Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia: a randomized clinical trial. JAMA Psychiatry. 2015;72(8):822–829.

Schreiner A, Aadamsoo K, Altamura AC, et al. A randomized, active-controlled rater-blinded 2-year study of paliperidone palmitate versus investigators' choice of oral antipsychotic monotherapy in patients with schizophrenia (prosipal). Poster LP-01-013. Poster presented at the 29th International College of Neuropsychopharmacology (CINP) World Congress of Neuropsychopharmacology; June 22–26, 2014; Vancouver, British Columbia, Canada.

Long-acting Injectables (LAIs): why not

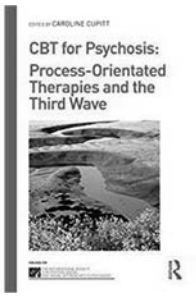
- Many physicians feel that they are not suitable for those with first-episode psychosis or early psychosis.
- How we talk about medicines matters. One study showed that:
  - 11/33 refused but when LAIs presented negatively
  - 27/28 though initially declined, agreed with their physicians to start these and see how they go when presented with more information and more positively
- Some reasons to avoid LAIs
  - Lack of resources to make certain people can receive their injections
  - Needle-phobia
  - Inadequate trial periods of oral medications
  - History of NMS an inability to monitor closely
  - Financial barriers
  - Plan to taper

Outpatient Treatment

Recommendations for On-going Care

Individual Psychotherapy for Psychosis

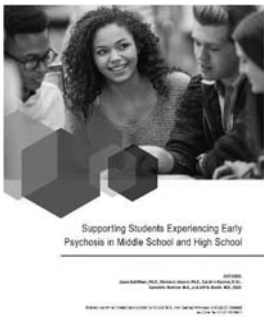
- Contemporary CBT and emerging therapeutic approaches involve an emphasis on one's relationship to their mind
- Mentalizing: you have a mind, I have a mind
- Metacognitive Training: accepting mental phenomenon as not something one must control (Ego bolstering)
- Mindfulness Practice: bringing one's awareness to thoughts, voices, sensations both those deemed "psychotic" and not, de-emphasizing attribution/meaning-making
- Committing to Have A Different Relationship to One's Mental Experience: behavior change
- Compassion Focused Therapy



Some tips:

- Offer mentalistic scaffolding: "We're here to talk about your relationship to your mind."
- Normalize voices and non-verbal auditory hallucinations: "What do you think this noise is trying to signal to you? What do you draw from this experience?" opposed to "Where do you think it comes from?"
- Use yourself: "When that happened, I had the thought in my mind _____. What occurred in your mind?"
- Pause and reflect, announcing that you are doing so…"sorry for my silence, in that moment I was just thinking about what you said."
- Offer reassurance: "I'm not trying to convince you of something or here to tell you that you are right or wrong. I am here so that we might learn from what happens in your life and you might take a different approach to your voices/ideas/feelings. One that helps you achieve your goals (school, work, relationships)."

Academic Support



- School-based counseling
- Medication accommodations
- Identifying triggers (loud noises in gym, the din of cafeteria voices)
- Providing alternative, quiet space at school for study or exams
- Extra time to complete exams
- Flexible deadlines
- In class support including executive function support with an emphasis on skills versus product
- Alternatives to public speaking
- Extra time to complete exams

https://www.nasmhpd.org/sites/default/files/Guidance_Document_Supporting_Students.pdf.

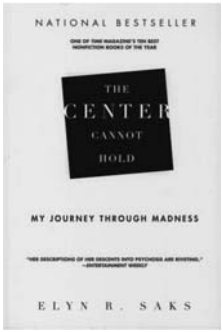
Family Support Part 1

- Believe in your power
- One step at a time
- Consider using medication to protect your future…
- Reduce stresses for a while
- Anticipate life stress
- Keep it calm
- Give each other space
- Set a few simple limits
- Solve problems step by step

http://www.easacommunity.org/PDF/p.846.2-familyguidelines_jun2012.pdf.

Family Support Part 2

- Connect with others and learn more through NAMI's Family-To-Family
  - www.nami.org
- *The Complete Family Guide to Schizophrenia: Helping Your Love One Get the Most Out of Life* by Kim T Mueser and Susan Gingerich
- *The Center Cannot Hold: My Journey Through Madness* by Elyn Saks



Medication Blueprint

- Continue LAI treatment for now
- Aim for functional recovery opposed to symptom amelioration only
- Considering a plan for tapering and discontinuing antipsychotics: "This is a temporary treatment. We're not planning on this forever." *
- Balancing need for calming agents while also recognizing habit-forming quality/dependence-generation with benzodiazepines
- Monitoring closely for side-effects: BMI, Fasting Lipids, AIMS, Akathisia review

EASA Medication Guide available at: http://www.easacommunity.org/PDF/easa-med-guide.pdf

[redacted]

[redacted]

Why taper?

*One study looked at 7-year follow-up of patient with FEP:

- Following up with 103 patients out of an original study of 128 wherein individuals were divided into a discontinuation/reduction (DR) group and maintenance therapy (MT) group
- Recovery occurred in:
  - DR = 40.4%
  - MT = 17.6%
  - Initial relapse rates in the DR group were twice as high over the first three years, then evened out.
- This suggests that one should not be "scared away" by relapses precipitated by tapering/discontinuations.
- Consider instead--in the first three years—trying to reduce and stop D2 blocking therapy while maximizing psychosocial support and providing short-term med therapy through these relapses/exacerbations.

Wunderink l, Nieboer RM, Wiersma D, Systema S, Nienhuis FJ. Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial. JAMA Psychiatry, 2013;70(9):913-20

What we discussed…

1) Clinical High Risk (CHR)

- Attenuated psychotics symptoms
- Social, emotional, and cognitive functioning deficits
- Approximately a 20% risk of conversion to psychosis within two years

2) List three "go to" or first-line agents to address the symptoms of psychosis (best initiated alongside other supports at **<72 weeks**)

- Aripiprazole
- Lurasidone
- Quetiapine?

3) Describe two advantages and two disadvantages of utilizing long-acting injectable (LAI) medications

- + Reduced relapses/exacerberations
- + Improved adherence, longer time to d/c
- - Economic and practical hurdles
- - Stuck with side-effects (may still have to take PO meds like benzotropine)
- Less dose-adjustment/strategy maneuverability

4) Utilize materials from this grand rounds for psychoeducation with families

- Go to www.EASAcommunity.org

5) List principles of emerging CBTp to help young people, transition age youth, and adults who are impacted by psychosis

- Mentalizing: "Mind-mindedness"
- Metacognitive Training: Acceptance
- Mindfulness Training: Awareness
- Commitment: Operating in new ways

Thanks to…

- My incredible CAP Fellows who inspire me…
- Todd Eisenberg, MD
- Carrie Milligan, MD
- Grand Rounds Committee led by Stephanie Lopez, MD & Sean Stanley, MD
- EASA Center for Excellence Team Members Ryan Melton, Tamara Sale, Katherine Hayden-Lewis, Julie Magers, Megan Sage, Christina Wall, Halley Doherty-Gary, Tania Kneuer
- **My patients and their families: always my greatest teachers**

OHSU SPH

Comments - Questions?

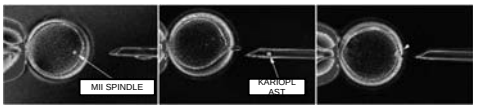
Please complete evaluation and provide feedback to receive CME

Human Germline Gene Therapy

Paula Amato, MD
Mitalipov Lab
Oregon Health & Science University

Germline Gene Therapy

- mtDNA → Mitochondrial Replacement Therapy

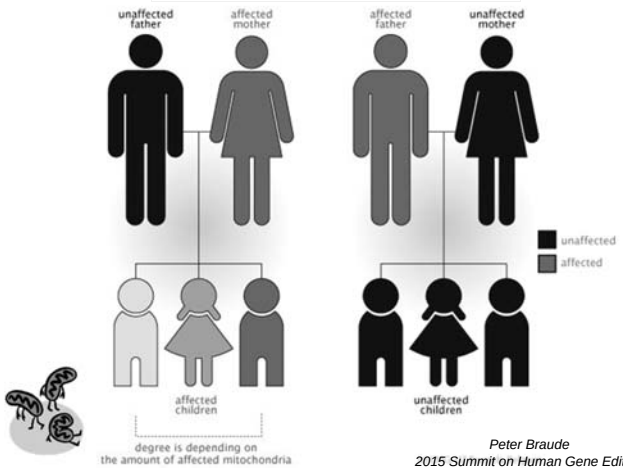


- nDNA → Nuclear Gene Correction

Prevention of Genetic Disease Strategies

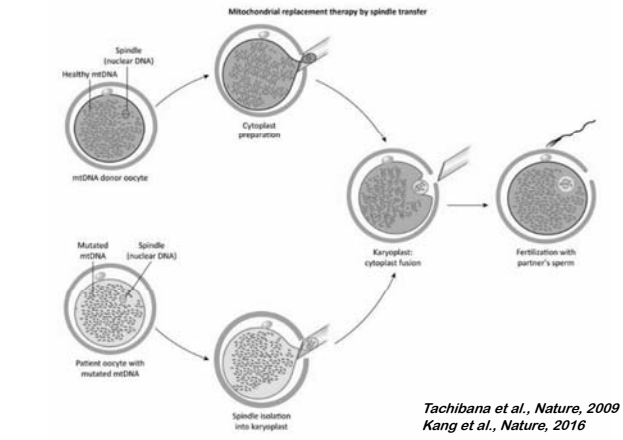
- Adoption
- Oocyte, sperm, or embryo donation
- Preimplantation genetic diagnosis (PGD)
- Germline gene therapy
  - Prevention of genetic disease transmission by correcting disease-causing gene mutations in reproductive cells (sperm, oocyte, or embryos)

mtDNA disease Inheritance

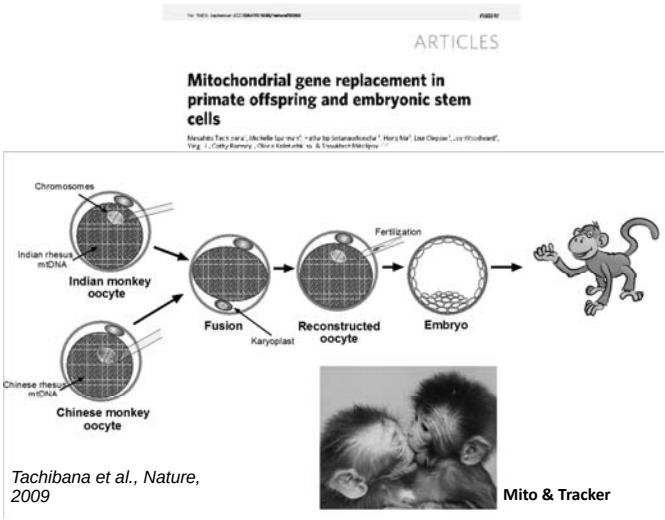


Peter Braude
2015 Summit on Human Gene Editing

Mitochondrial Replacement Therapy
Spindle Transfer between MII oocytes



Tachibana et al., Nature, 2009
Kang et al., Nature, 2016



Tachibana et al., Nature, 2009

Mito & Tracker

Germline transmission of donor mtDNA to F2 offspring

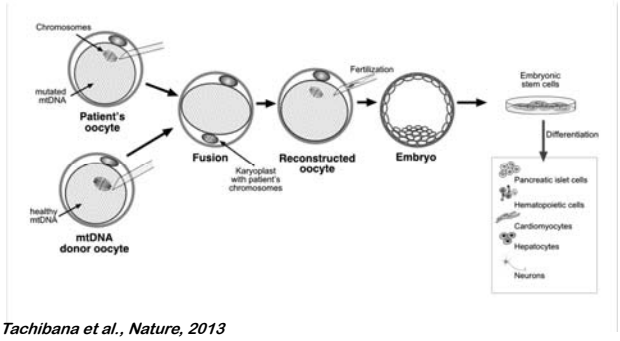
Van Dyken et al., unpublished

ARTICLE

doi:10.1038/nature11647

Towards germline gene therapy of inherited mitochondrial diseases

Masahito Tachibana[1], Paula Amato[2], Michelle Sparman[1], Joy Woodward[1], Dario Melguizo Sanchis[1], Hong Ma[1], Nuria Marti Gutierrez[1], Rebecca Tippner-Hedges[1], Eunju Kang[1], Hyo-Sang Lee[1], Cathy Ramsey[2], Keith Masterson[2], David Battaglia[2], David Lee[2], Diana Wu[1], Jeffrey Jensen[2,3], Phillip Patton[2], Sumita Gokhale[4], Richard Stouffer[2,3] & Shoukhrat Mitalipov[1,2]



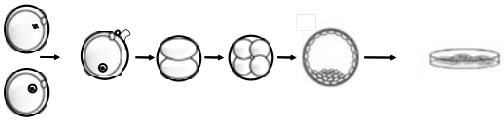
Tachibana et al., Nature, 2013

LETTER

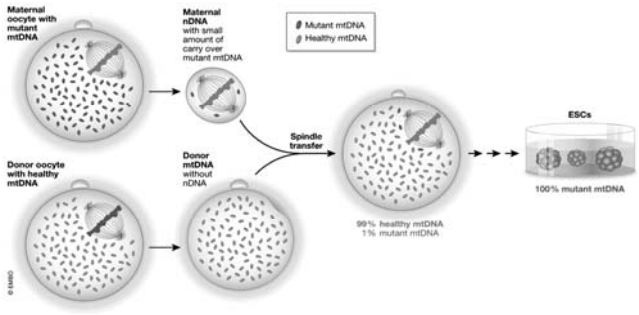
doi:10.1038/nature20592

Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations

Eunju Kang[1,2], Jun Wu[1], Nuria Marti Gutierrez[1,2], Amy Koski[1,2], Rebecca Tippner-Hedges[1,2], Karen Agaronyan[1], Aida Platero-Luengo[3], Paloma Martinez-Redondo[3], Hong Ma[1,2], Yeonmi Lee[1,2†], Tomonari Hayama[1,2], Crystal Van Dyken[1,2], Xinjian Wang[2], Shiyu Luo[3], Riffat Ahmed[1,2], Ying Li[1,2], Dongmei Ji[1,2], Refik Kayali[2], Cengiz Cinnioglu[2], Susan Olson[4], Jeffrey Jensen[4], David Battaglia[4], David Lee[4], Diana Wu[4], Taosheng Huang[5], Don P. Wolf[2,3], Dmitry Temiakov[6], Juan Carlos Izpisua Belmonte[1], Paula Amato[4] & Shoukhrat Mitalipov[1,2,3,7]



Reversal Back to Maternal mtDNA



Wolf et al., EMBO J. 2017

Mitochondrial Replacement Therapy

- Replacement of entire mt genome
- Applicable to any mtDNA mutation type
- Preclinical animal studies demonstrate safety and efficacy
- Some ESCs (15%) demonstrated loss of donor mtDNA and reversal to the maternal haplotype
- Haplotype-matching may be required
- Clinical trials ongoing in the UK; preclinical studies in U.S.
- Several births reported worldwide

ARTICLE

doi:10.1038/nature23305

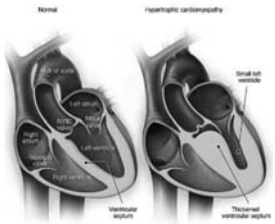
Correction of a pathogenic gene mutation in human embryos

Hong Ma[1]*, Nuria Marti-Gutierrez[1]*, Sang-Wook Park[2]*, Jun Wu[3]*, Yeonmi Lee[1], Keiichiro Suzuki[3], Amy Koski[1], Dongmei Ji[1], Tomonari Hayama[1], Riffat Ahmed[1], Hayley Darby[1], Crystal Van Dyken[1], Ying Li[1], Eunju Kang[1], A.-Reum Park[2], Daesik Kim[4], Sang-Tae Kim[2], Jianhui Gong[5,6,7,8], Ying Gu[5,6,7], Xun Xu[5,6,7], David Battaglia[1,9], Sacha A. Krieg[9], David M. Lee[9], Diana H. Wu[9], Don P. Wolf[4], Stephen B. Heitner[10], Juan Carlos Izpisua Belmonte[3]§, Paula Amato[1,9]§, Jin-Soo Kim[2,4]§, Sanjiv Kaul[10]§ & Shoukhrat Mitalipov[1,10]§

Genome editing has potential for the targeted correction of germline mutations. Here we describe the correction of the heterozygous *MYBPC3* mutation in human preimplantation embryos with precise CRISPR–Cas9-based targeting accuracy and high homology-directed repair efficiency by activating an endogenous, germline-specific DNA repair response. Induced double-strand breaks (DSBs) at the mutant paternal allele were predominantly repaired using the homologous wild-type maternal gene instead of a synthetic DNA template. By modulating the cell cycle stage at which the DSB was induced, we were able to avoid mosaicism in cleaving embryos and achieve a high yield of homozygous embryos carrying the wild-type *MYBPC3* gene without evidence of off-target mutations. The efficiency, accuracy and safety of the approach presented suggest that it has potential to be used for the correction of heritable mutations in human embryos by complementing preimplantation genetic diagnosis. However, much remains to be considered before clinical applications, including the reproducibility of the technique with other heterozygous mutations.

MYBPC3 Mutation Causes Hypertrophic Cardiomyopathy

- Late onset, autosomal dominant disease
- Causes hypertrophic cardiomyopathy (HCM); prevalence in general population is 1:500
- Deletions in MYBPC3 account for ~35% of all cases of HCM



Patient

- Male with Hypertrophic Cardiomyopathy
- MYBPC3 mutation (4bp deletion), c.1420_1423 GAGT deletion
- Heterozygous

Wild-type allele: cgggtggagttt**gagt**gtgaagtatcggagga
Mutant allele : cgggtggagttt----gtgaagtatcggagga

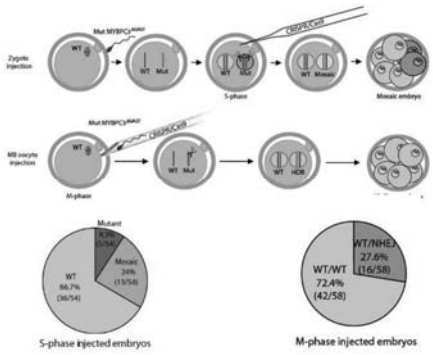
CRISPR/Cas9

- **Cas9 nuclease**
- **Guide RNA:** 5′-ggtggagtttgtgaagtat-3′
- **DNA Template (190bp)**

agatggcctcaggggagccaaccctcatgctcaccctgcctggacagagccccctgtgctcatc
acgcgcccctggaggaccagctggtgatggtggggcagcgggtggagttt**gagt**gc**g**a**g**gtat
cggaggaggggcgcaagtcaaatggtgagttccagaagcacggggcatgggtgttgggggc

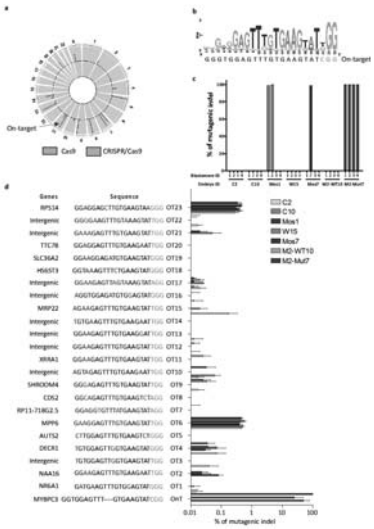
Bold: Mutation, Blue: PAM sequence, Red: marker SNPs

DNA Repair Outcomes and Mosaicism



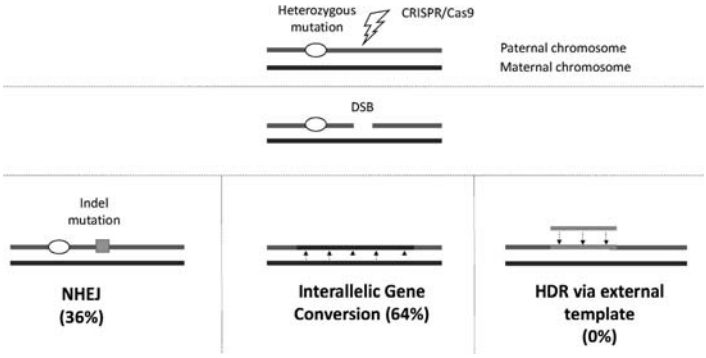
Ma et al., Nature 2017

Off-Target Effects

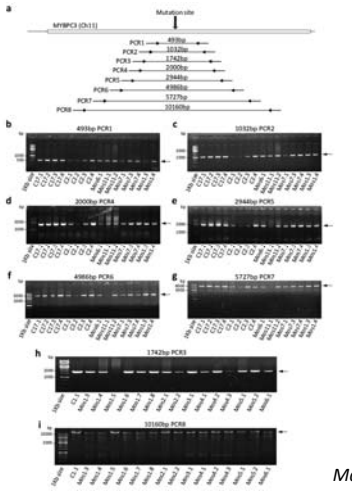


Ma et al., Nature 2017

GENE CONVERSION heterozygous mutations



Ma et al., Nature 2017, 2018

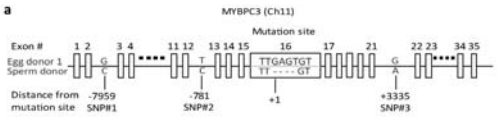


Ma et al., Nature 2018

BRIEF COMMUNICATIONS ARISING

Ma et al. reply

REPLYING TO D. Egli et al. *Nature* **560**, https://doi.org/10.1038/s41586-018-0379-5 (2018); F. Adikusuma et al. *Nature* **560**, https://doi.org/10.1038/s41586-018-0380-z (2018)



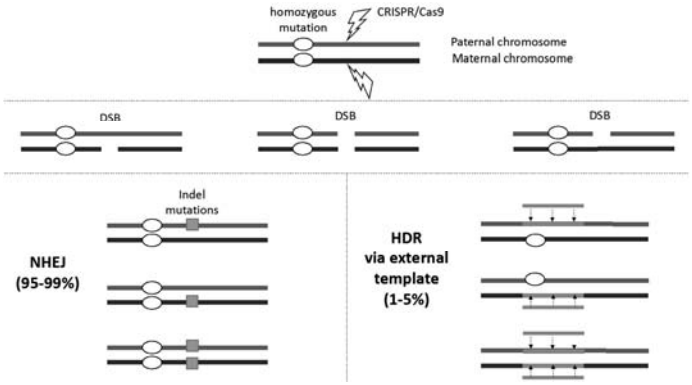
b

Sample	MYBPC3 genotype	SNP #1	SNP #2	SNP #3
Egg donor 1	WT/WT	G	T	G
Sperm donor	WT/Mut	C	C	A
WT 4.1	WT/WT	G/C	T/C	G/A
Mos 2.3	WT/NHEJ	G/C	T/C	G/A
Mos 3.2	WT/NHEJ	G/C	T/C	G/A
Mos 2.1	WT/HDR	G	T	G
Mos 3.1	WT/HDR	G	T	G
Mos 2.2	WT/HDR	G/C	T	G/A

Conversion tract

Ma et al., Nature 2018

Molecular Mechanisms of DNA Repair homozygous mutations



Liang et al., unpublished

Germline Gene-Editing Summary

- High targeting efficacy
- High efficiency of repair by gene conversion
- Results have been independently replicated
- Applicable to heterozygous mutations only
- Complements conventional PGD by rescuing mutant embryos
- Advantages over conventional treatments including somatic gene therapy (more cost-effective)
- Efficiency and safety must be improved and ethical issues addressed before moving to clinical trials

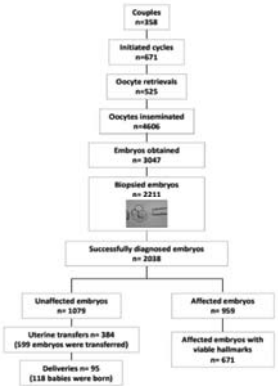
Human Genome Editing

Science, Ethics, and Governance

- Absence of reasonable alternatives
- Restriction to preventing a serious disease or condition
- Restriction to editing genes that have been convincingly demonstrated to cause or to strongly predispose to the disease or condition
- Restriction to converting such genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects
- Availability of credible pre-clinical and/or clinical data on risks and potential health benefits of the procedures
- Ongoing, rigorous oversight during clinical trials of the effects of the procedure on the health and safety of research participants
- Comprehensive plans for long-term, multigenerational follow-up while still respecting personal autonomy
- Maximum transparency consistent with patient privacy
- Continued reassessment of both health and societal benefits and risks, with broad on-going participation and input by the public
- Reliable oversight mechanisms to prevent extension to uses other than preventing a serious disease or condition

Could Failure in Preimplantation Genetic Diagnosis Justify Editing the Human Embryo Genome?

Steffann et al, Cell Stem Cell, 2018



Future Directions

- MRT clinical trials
- MRT for other indications eg age-related infertility
- Germline gene editing targeting other gene mutations eg BRCA
- Insights into novel DNA repair mechanisms in human embryo → somatic gene therapy applications for chronic degenerative diseases of aging and cancer?

Center for Embryonic Cell and Gene Therapy

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Riffat Ahmed
Crystal Van Dyken
Hayley Darby
Don Wolf
Masahito Tachibana
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Dongmei Ji

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REI-OBGYN

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KCVI
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Taosheng Huang
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Thank You

Behavioral Management of Insomnia in Primary Care

Teni Davoudian, PhD
Assistant Professor in Psychiatry & Ob/Gyn
OHSU Center for Women's Health
February 14, 2019

Diagnostic Criteria

- **Symptoms**
  - Difficulties falling asleep
  - Difficulties staying asleep
  - Waking up earlier than intended time
  - Negative impact on daytime functioning
- **Duration**
  - 3x/week for 3+ months
- **Prevalence**
  - 6-10% of population meet criteria
  - More prevalent among women
  - 10-20% of PCP visits related to insomnia

American Psychiatric Association, 2013

Hormonal Factors

- **Menstrual Cycle**
  - Luteal phase insomnia
    - Longer sleep latency, lower sleep efficiency, and lower sleep quality
    - Progesterone withdrawal
    - Changes in core body temperature
  - Severity of PMDD and dysmenorrhea associated with perceived severity of insomnia
- **Perimenopause**
  - Reduction of progesterone, estrogen, and melatonin

Freeman et al., 2004; Moline et al., 2004

Psychosocial Burdens of Insomnia

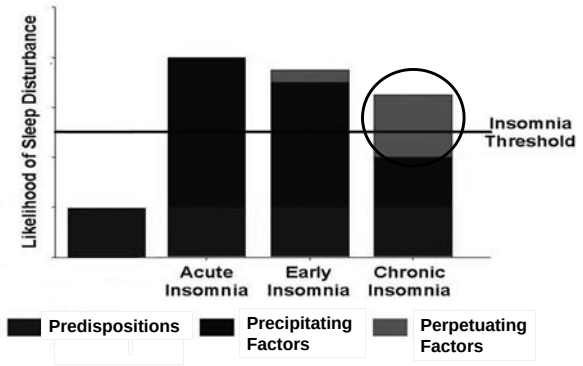
- Sleep disruptions are common in several mental illnesses
- Insomnia can persist despite psychotherapy and psychopharmacological interventions for depression and anxiety
- Depression with insomnia associated with higher:
  - Severity of depression
  - Risk of suicide
  - Attrition from treatment
  - Depression relapse rates
- High societal cost of insomnia

Carney et al., 2007; Manber et al., 2008; Ozminkowski et al., 2007

Development of Chronic Insomnia

1. **Predisposition**
   - Gender
   - Personality
   - Genetics
   - Mental health conditions
   - Medical conditions
2. **Precipitating Factors**
   - Trauma
   - Shift work
   - Frequent travels
   - Hormonal fluctuations

- **Perpetuating Factors**
  - Cognitive distortions about sleep
  - Naps
  - Sleeping in to "catch up"
  - Low level of physical activity
  - Using alcohol to fall/stay asleep
  - Noncompliance with CPAP/BIPAP machine

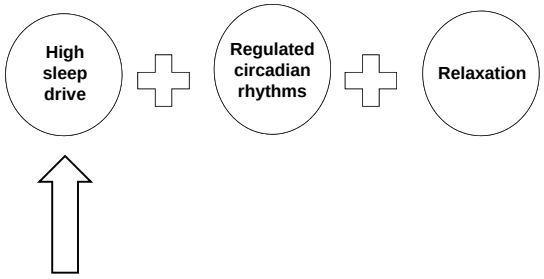


CBTI: Safety and Efficacy

- Contraindications: bipolar and seizure disorders
- More effective than sleep meds in reducing sleep latency
- Longer lasting gains compared to med management of insomnia
- Recommended as the first-line of treatment by:
  - National Institutes of Health
  - American College of Physicians
  - Academy of Sleep Medicine

Castronovo et al., 2017: McCrae et al., 2014; Smith et al., 2002; Trauer et al., 2015 Watanabe et al., 2015

Ingredients of Good Sleep

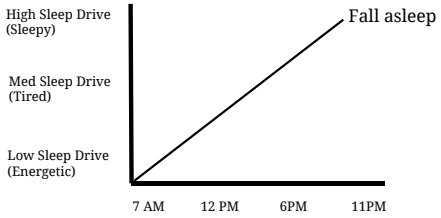


Sleep Drive

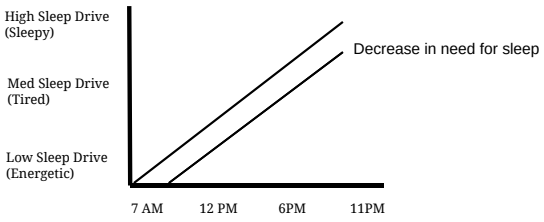
- Buildup of "pressure" to sleep
- Sleep drive accumulates when awake and diminishes during sleep
- Byproduct of energy expenditure
- Impacted by:
  - Level of physical activity throughout the daytime
  - Inconsistent wakeup time ("social jet lag")
  - Naps

Dworak et al., 2007; Huang et al., 2014

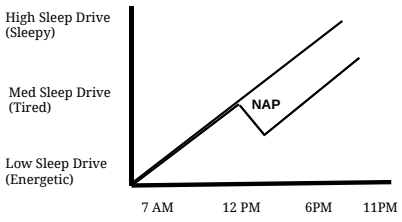
Buildup of Sleep Drive



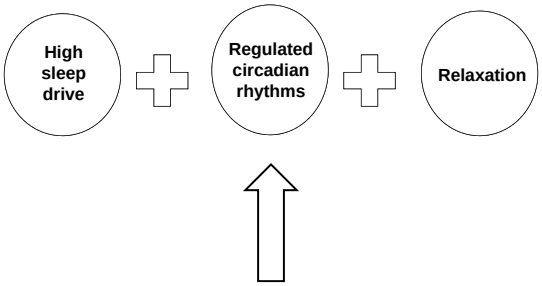
Buildup of Sleep Drive



Buildup of Sleep Drive



Ingredients of Good Sleep



Circadian Rhythms

- **Synchronized by environmental clues**
  - Body temperature
  - Exposure to light
- **Exposure to light**
  - Release of neurotransmitters that promote wakefulness ("alerting signals")
  - Reduced production of melatonin
  - Smartphones, computers, tablets
    - Blue light filers do not improve subjective sleep quality
- **Exposure to dimness/darkness**
  - Reduced secretion of alerting signgnals
  - Increased melatonin production
- Rule of the 4s: no alcohol, heavy meals, or cardio exercise within 4 hours before bedtime

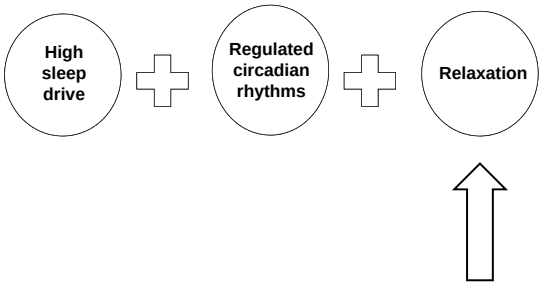
Lawrence et al., 2017; Laders et al., 2009

Circadian Chronotypes: Owls vs. Larks

- **Larks**
  - Not immune to insomnia but their sleep patterns match society's schedule
  - More regularity in daily lifestyle
- **Owls**
  - Higher levels of daytime sleepiness
  - Spend more time in bed
  - More concerns about the consequences of insomnia
  - Spend more time with electronics prior to bedtime
  - Associated with major depressive disorder

Chan et al., 2014; Fossum, et al., 2014; Merikanto et al., 2012; Ong et al., 2017

Ingredients of Good Sleep



Pre-sleep Hyperarousal

- Contributes to development and maintenance of insomnia
- Evolutionarily adaptive to not fall asleep when stressed
- Overrides sleep drive and circadian systems
- Stress and relaxation are opposing systems
- Increases subjective estimation of sleep latency

Clock Watching

- "The dreaded countdown"
- Increases pre-sleep hyperarousal
- Losing hours of sleep thinking about how many hours of sleep you're losing

Sleep Effort

- Attempt to control sleep
- Increases hyperarousal and severity of sleep disturbance
- Becomes its own source of stress
- If you can't sleep, stop trying

Fairholme & Manber, 2014

Middle-of-Night Awakenings

- Repeated pairing of bed with stress in the middle of the night
- Association between bed and stress builds outside of our awareness
- Unknowingly train ourselves to be awake in bed (conditioned arousal)

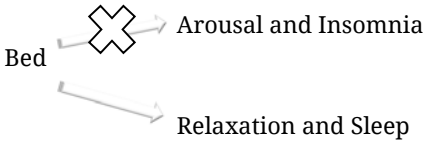
- You've likely associated your bed with stress if any of these statements sound familiar to you:
  - I'm watching TV in the evenings and I fall asleep. Once I get up and go to bed, I'm wide awake.
  - As soon as I turn the lights out and get into bed, my mind starts racing.
  - I sleep better when I'm away from home.
  - I dread going to bed.

Stimulus Control

- Treatment for middle-of-night awakenings:

1. **Step 1:**
   - Let go of any personal rules regarding bedtime
   - Only go to bed when sleepy
   - No activities in bed other than sleep and sex
2. **Step 2:**
   - Get out of bed if 15 to 20 mins have passed
   - Engage in a relaxing activity
3. **Step 3:**
   - Go back to bed when sleepy (not just tired)
   - Repeat step 2 as many times as needed
4. **Step 4:**
   - Maintain consistent wakeup time regardless of sleep quantity and quality
   - Get out of bed

Stimulus Control



Cognitive Distortions about Sleep

- Sleep scapegoat
  - Contributing any and all uncomfortable physical/emotional sensations to insomnia
- Mixed research findings regarding insomnia and neuropsychological performance:
  - Mild to moderate impairments in problem solving, visual tracking, and reaction time
  - No significant impact on divided attention, sustained attention, verbal fluency, and cognitive flexibility
- Discordance in subjective reports of daytime insomnia-induced impairment and objective measures of performance
- Patients with insomnia are particularly vigilant of potential consequences of insomnia
- Are the insomnia-related cognitive deficits partially due co-morbid psychiatric conditions?

Fortier-Brochu et al., 2012; Orf et al., 2007; Varkevisser et al., 2007

ETOH

- Hastens onset of sleep
- Shallow sleep with multiple awakenings
  - GI upset, sweating, dehydration
- Decreased REM sleep during the first half of the night
- Worsening of sleep apnea

Summary of Insomnia Interventions

- Wake up at same time every morning
- Only go to bed when sleepy (not just tired)
- Get out of bed if you haven't fallen asleep within 15-20 mins
- Reduce sleep effort
- Reduce clock watching
- Relaxation training
- Remember, you do not have to do these interventions forever!

Insomnia & Relaxation Resources

- Apps:
  - CBTI-Coach
  - Pzizz
  - Sleep Genius
  - Relax Me
  - Calm
  - Head Space
  - Yoga for Insomnia

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Thank You

Diabetes in the Older Adult

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Harold Schnitzer Diabetes Health Center
Oregon Health & Science University
February 14th, 2019
50th Annual Primary Care Review

Disclosures:

- I have nothing to disclose

Learning points:

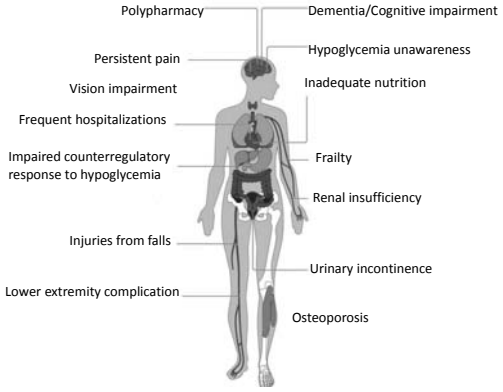
1. Review complications and comorbidities in older adults with diabetes
2. Review areas of special focus for lifestyle management in older adults with diabetes
3. Strategies for individualizing glycemic targets for older adults
4. Treatment approaches: oral medications, insulin, continuous glucose monitoring
5. Applying these approaches to patient cases

Size of the issue

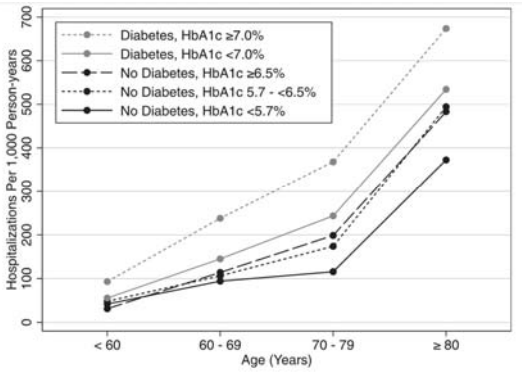
- ~25% of people over the age of 65 years have diabetes
- ~50% older adults have prediabetes
- These numbers are expected to increase in coming years
- In 2012, 104 billion (59%) of the estimated $176 billion in United States healthcare expenditures attributable to older adults with diabetes

Can J Diabetes. 2016 Feb;40(1):66-72.
Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

What is unique about diabetes in the older adult?



Longitudinal data on all-cause hospitalizations by A1C



Rates of hospitalization 3.1x higher in those with diabetes vs. those without

Diabetes Care 2017;40:509–517

Hypoglycemia

- Aging impacts counter-regulation to hypoglycemia
  - reduced glucagon, epinephrine, growth hormone response lessen symptoms and impair rise in glucose
- Aging changes pharmacokinetics of oral medications and insulin
  - drug absorption, distribution, renal elimination
- Other issues: Alcohol ingestion, exercise, weight loss, renal or liver disease, fasting or missing meals, multiple daily injections of insulin, cognitive deficits leading to self management deficits
- Hypoglycemia can increase risk of cardiovascular events

Can J Diabetes. 2016 Feb;40(1):66-72.
Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

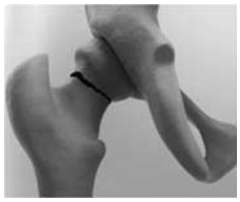
Hypoglycemia

- Bidirectional relationship between hypoglycemia and dementia
  - Patients hypoglycemia have increase the risk for dementia
  - Cognitive impairment increases risk for hypoglycemia
- Hypoglycemia events may prompt need for adjustment of glycemic goals
- Just increasing the A1c goal does not necessarily decrease risk of hypoglycemia (more on this later)

Can J Diabetes. 2016 Feb;40(1):66-72.
Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

Osteoporosis and Fractures

- Hip fractures in older adults: 25% risk of mortality in the following year
  - Loss of independence, financial hardship, increased overall risk of death.
- People T2DM have normal to high BMD compared with their age-matched healthy peers (M+W)
- Despite higher BMD, both men and women with diabetes are at an increased risk of fracture
  - T1DM: relative risk 6.3
  - T2DM: relative risk 1.7
- Assess fracture history and risk factors and recommend DEXA if appropriate
- Fracture prevention: vitamin D supplementation, dietary calcium, weight bearing exercises
- For high risk patients: Avoid TZDs and SGLT2s due to association with fractures



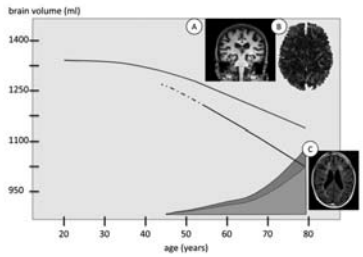
Curr Opin Endocrinol Diabetes Obes. 2012 Apr; 19(2): 128–135.
Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

Physical Activity

- Flexibility training and balance training are recommended 2–3 times/week for older adults with diabetes.
- Yoga and tai chi may be included based on individual preferences to increase flexibility, muscular strength, and balance.
- Clinical trials show A1C-lowering from resistance training in older adults with type 2 diabetes

Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

Brain changes with diabetes



- Type 2 diabetes is associated with global brain atrophy at rate up to 3x higher than age matched controls
- MRI studies have shown patients with T1D of >30 years of duration match that of T2D of ~7 years of duration

Diabetes 2014;63:2244– 2252 | DOI: 10.2337/db14-0348
Cognitive Dysfunction in Older Adults With Diabetes Diabetes Care Volume 40, April 2017

Cognitive impairment

- Consider screening older adults (aged >65 years) with diabetes for cognitive impairment and depression. (Grade of evidence: B)
- Higher incidence of dementia (1.5-2.5x), Alzheimer's disease, vascular dementia
- Poor glycemic control is associated with decline in cognitive function
- Impairs ability for patient to do complex self—management tasks (glucose monitoring, adjusting insulin doses, timing/content of diet)
- Critical to simplify regimens and involve caregivers

Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147
Cognitive Dysfunction in Older Adults With Diabetes Diabetes Care Volume 40, April 2017

Clinical presentations of cognitive dysfunction and strategies for management

Affected behavior	Impact on diabetes self-care	Strategies to improve management
Memory loss	• Forget to monitor glucose • Forget to take medications • Forget to take insulin injections • Forget to eat on time • Forget to eat before exercise • Forget to attend clinic visits	• Decrease frequency of self-monitoring, check when caregivers are available • Pillboxes, alarms • Long-acting formulations to decrease frequency of pills/day • Decrease number of insulin injections • Involve caregivers • Choose supervised exercise programs • More than one clinic visit reminders
Problem-solving difficulty	• Seems to remember instructions but unable to integrate into practice • Unable to recognize or treat hypoglycemia	• Repeated education and instructions at each visit • Avoid labels such as "noncompliant" • Make small changes at a time • Avoid complex regimens
Difficulty stopping old behavior and starting new behavior	• Seems to be "stubborn" • Refuses any new therapy • Errors occur when old routines are changed	• Avoid changes if possible • Ask for help from caregivers with reminders when behavior is being changed • May need to restrict access to insulin (especially in type 1 patients) if too much insulin is taken due to old habits
Difficulty with mental flexibility	• Feel anxious regarding "failing" the treatment plans • Too much focus on diabetes management	• Avoid difficult tasks such as sliding scales • Simplify regimen • Decrease the need for frequent snacks or monitoring

Cognitive Dysfunction in Older Adults With Diabetes. Diabetes Care Volume 40, April 2017

Screening for complications

- Older adults have highest rates of amputation, MI, visual impairment and ESRD related to diabetes
- Screening for diabetes complications should be individualized in older adults
  - More screening in those with longer life expectancies
- Particular attention should be paid to complications that would lead to functional impairment
  - Eye exam (can be repeated every 2-3 years if initial exam normal)
  - Foot exam

Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147
Diabetes Care 2012 Dec; 35(12): 2650-2664

Management of comorbidities

Health status	A1c goal	Blood pressure	Lipid treatment
Healthy - Few coexisting chronic illness - intact cognitive and function status	<7.5%	<140/90	Statin unless contraindicated or not tolerated
Complex/intermediate -multiple coexisting chronic illnesses -2+ ADL impairments -Mild-mod cognitive impairment	<8.0%	<140/90	Statin unless contraindicated or not tolerated
Very complex/poor health -LTC or end-stage chronic illness -Mod-severe cognitive impairment - >2 ADL dependencies	<8.5%	<150/90	Consider likelihood of benefit (2º prevention > 1º prevention)

Looser A1c targets >8.5% (8.5%= average glucose 200mg/dl) are not recommended as the expose patients to risks of glycosuria, dehydration, HHS, and poor wound healing.

Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

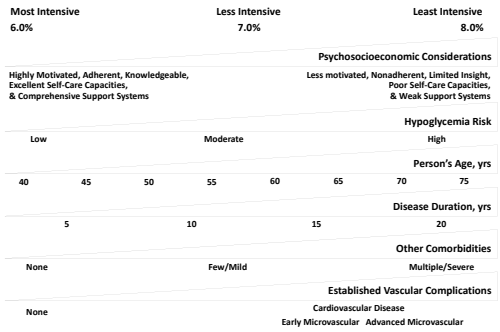
End-of-life Care

Recommendations from ADA:

- When palliative care is needed in older adults with diabetes, strict blood pressure control may not be necessary, and withdrawal of therapy may be appropriate.
- Intensity of lipid management can be relaxed, and withdrawal of lipid-lowering therapy may be appropriate.
- Overall comfort, prevention of distressing symptoms, and preservation of quality of life and dignity are primary goals for diabetes management at the end of life.

Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

Individualizing A1C Targets



Ismail-Beigi F, et al. Ann Intern Med. 2011;154:554-559.

Individualizing treatment goals

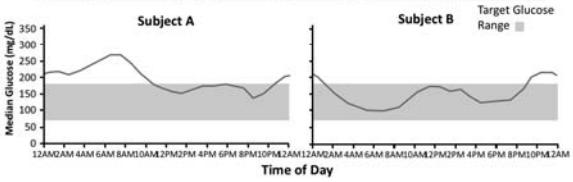
- Many conditions associated with increased red blood cell turnover which can falsely increase or decrease A1C can exist in older adults:
  - Hemodialysis
  - Recent blood loss or transfusion
  - Erythropoietin therapy
  - Anemia from iron, B12, folate deficiency
  - Chronic aspirin use
  - Chronic heavy opioid use, alcohol use, cigarette use
- In these instances, use CBGs for monitoring

J Gen Intern Med. 2014 Feb; 29(2): 388–394.

A1C Represents a Wide Range of Glucose Values

Different glucose excursions in people with A1C of 8%

Subject	Lab A1c	Glucose Exposure		Glucose Ranges		
		Average Glucose	Estimated A1c	Low	In Target Range	High
A	8.0%	195 mg/dL	8.4%	.5%	42.2%	57.3%
B	8.0%	156 mg/dL	7.0%	10.1%	54.5%	35.4%



Beck RW, et al. Diabetes Care. 2017;40:994-999.

A1C and Mean Glucose

- Data from 3 randomized clinical trials in people with type 1 or 2 diabetes (N = 387)
  - 20-78 yrs of age
  - 83% white
  - 19% type 2 diabetes

A1C, %	Estimated Mean Glucose, mg/dL
6	101-163
7	**128-190**
8	155-218
9	182-249
10	209-273

Beck RW, et al. Diabetes Care. 2017;40:994-999.

Keep in Mind….

- The therapy options for type 2 diabetes has changed drastically over the past 10 years
- Sulfonylureas and insulin have a higher risk of hypoglycemia than other newer agents (SGLT2s, DPP4s, GLP1RAs)
- Beware of therapeutic inertia and acceptability creep (7.5%->8.5%-> etc…)

74 y.o. Female with poorly controlled Type 2 Diabetes, CABG after MI in 2010, OSA on CPAP, HTN, and recent eye complication related to DM. Patient was diagnosed with diabetes in two years ago at age 72, with no symptoms.

Current diabetes meds: metformin 1000mg BID. Current A1c is 10%. Glucose is 309. She is now having polyuria and polydipsia. She is motivated to improve control. Never had hypoglycemia.

1. What is your A1c goal for this patient?

a. <6.5%
b. 7.5-8%
c. 8-9%
d. Other

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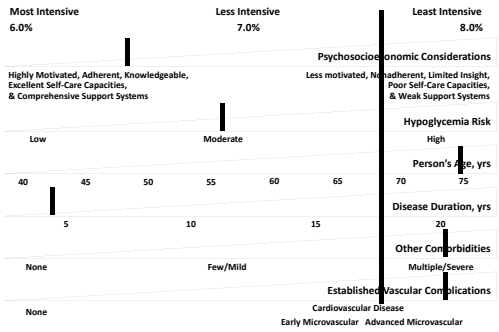
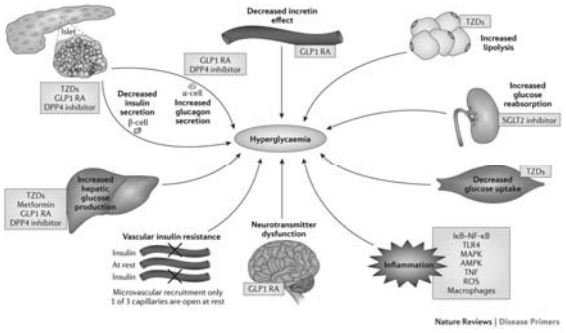
Individualizing A1C Targets



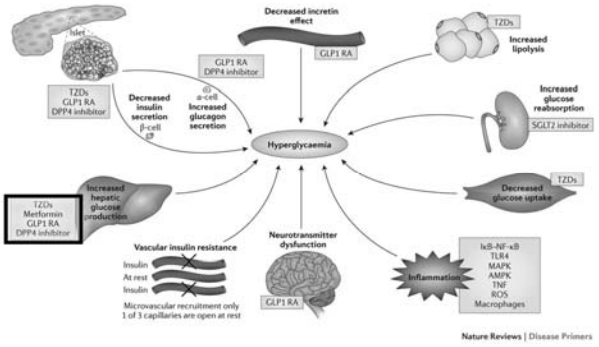
Ismail-Beigi F, et al. Ann Intern Med. 2011;154:554-559.

Management of oral diabetes medications



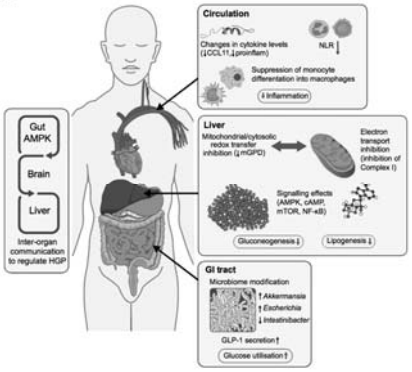
DeFronzo, R. A. *et al.* (2015) Type 2 diabetes mellitus *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.19

Metformin



DeFronzo, R. A. *et al.* (2015) Type 2 diabetes mellitus *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.19

Metformin



Diabetologia (2017) 60:1577–1585

Metformin

Benefits

- Oral
- Low risk of hypoglycemia
- Weight neutral
- Cheap
- Can now use down to GFR 30

Limitations

GI Side effects (nausea/diarrhea)

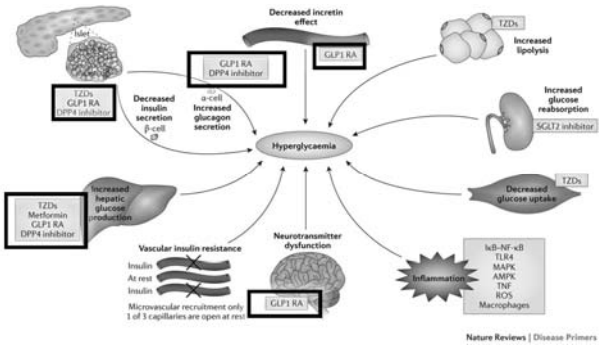
Potential for B12 deficiency (annual monitoring recommended)

American Diabetes Association. Diabetes Care. 2018;41:573-585.
Heerspink HJ, et al. Circulation. 2016;134:752-772.

Initiation/titration:

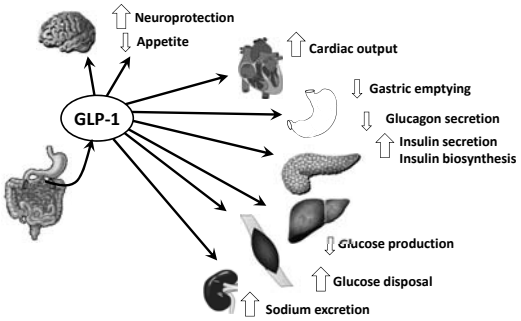
- Start low, go slow!
  - If patients have a bad experience with metformin at the beginning, they are very reluctant to try it again in the future
- Start with 500mg once daily with dinner meal for one week
- Increase to 500mg twice daily (with breakfast and dinner) for one week
- Then 500mg with breakfast, 1000mg with dinner for one week
- Then up to target dose of 1000mg twice daily
  - If symptoms of diarrhea or stomach upset, drop dose by 500mg
  - If issues with diarrhea or stomach upset despite this titration schedule, then try an extended release metformin formulation
  - If patient can only tolerate 1000mg daily, that is better than nothing!

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists



DeFronzo, R. A. *et al.* (2015) Type 2 diabetes mellitus. *Nat. Rev. Dis. Primers*

GLP1 Receptor Agonists



Campbell RK, et al. J Family Pract. 2009;59(suppl 1):S5-S9.
DeFronzo RA. Med Clin N Am.2004;88:787–835.
Gallwitz B. *Rev Diabet Stud*. 2009;6:247-259.

GLP-1 Receptor Agonists

- FDA-approved agents: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide

Benefits

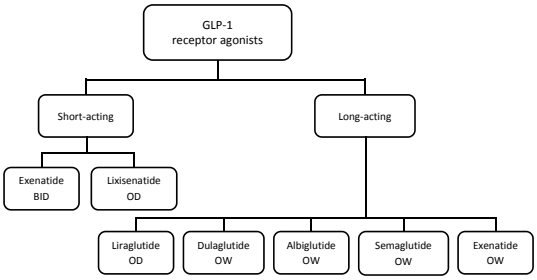
- Cardioprotective (liraglutide, semaglutide)
- Low risk of hypoglycemia
- Weight loss common
- Minimal titration

Limitations

- Potential side effects (eg, nausea, vomiting, diarrhea)
- Injectable (although pain is minimal)
- ?Pancreatitis risk
- Medullary thyroid cancer risk

American Diabetes Association. Diabetes Care. 2018;41:S73-S85.
Madsbad S. Diabetes Obes Metab. 2016;18:317-332.
Zaccardi F, et al. Ann Int Med. 2016;164:102-113.

GLP-1 Receptor Agonists



BID, twice daily; GLP-1, glucagon-like peptide-1; OD, once daily; OW, once weekly.

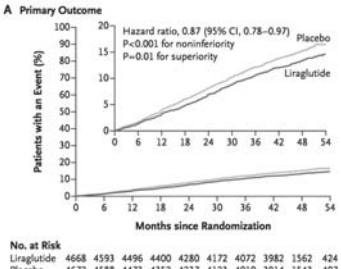
GLP-1 Receptor Agonists

Initiation/Titration:

- Warn patients of possible nausea, diarrhea in first few days of starting this medication
- Package inserts provide a titration schedule, follow this!
- Be sure that patients start with lowest dose
- If patients have GI side effects with up titration, have them decrease back to the last tolerated dose

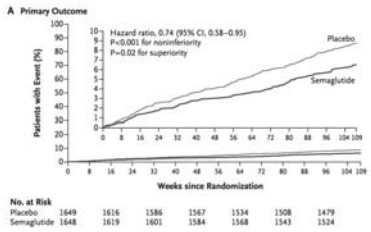
Cardiovascular Outcomes GLP1-RA

Primary Outcome: CV Mortality, Nonfatal MI, or Nonfatal Stroke



LEADER: Liraglutide randomized, double-blind, multicenter phase III trial in pts with type 2 diabetes and high CV risk (N = 9340)

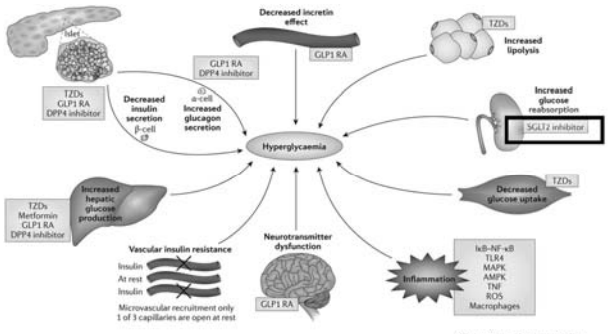
Marso SP, et al. N Engl J Med. 2016;375:311-322.



SUSTAIN-6: Semaglutide randomized, double-blind, multicenter phase III trial in pts with type 2 diabetes and high CV risk (N = 3297)

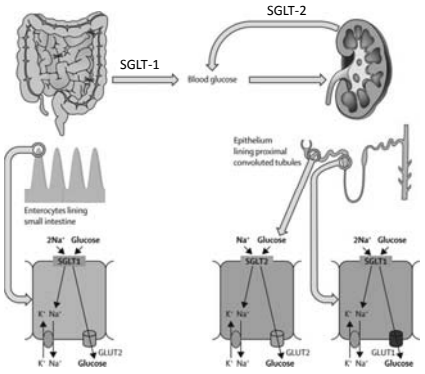
Marso SP, et al. N Engl J Med. 2016;375:1834-1844.

SGLT2 Inhibitors



DeFronzo, R. A. *et al.* (2015) Type 2 diabetes mellitus *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.19

Sodium-glucose linked transporter (SGLT)



The Lancet. 2013; 1: 140-51

SGLT-2 Inhibitors

- FDA-approved agents: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin

Benefits

- Oral
- Cardioprotective (canagliflozin, empagliflozin)
- Low risk of hypoglycemia
- Weight loss
- Decreased blood pressure

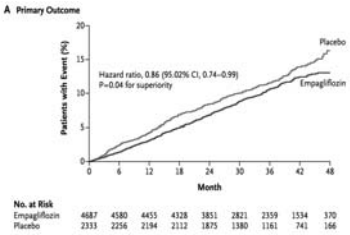
Limitations

- Genitourinary infections
- Risk of volume depletion
- Risk of diabetic ketoacidosis
- Increased risk of amputation in high-risk pts (with canagliflozin)

American Diabetes Association. Diabetes Care. 2018;41:573-S85.
Heerspink HJ, et al. Circulation. 2016;134:752-772.

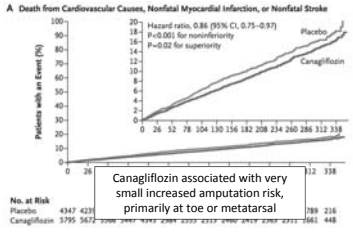
Cardiovascular Outcomes for SGLT2 Inhibitors

Primary Outcome: CV Mortality, Nonfatal MI, or Nonfatal Stroke



EMPA-REG: Emagliflozin, randomized, double-blind, multicenter phase III trial in pts with type 2 diabetes and CVD (N = 7020)

Zinman B, et al. N Engl J Med. 2015;373:2117-2128.



Canagliflozin associated with very small increased amputation risk, primarily at toe or metatarsal

CANVAS/CANVAS-R: Canagliflozin, randomized, double-blind, multicenter phase III/IV trials in pts with type 2 diabetes and high CV risk (N = 10,142)

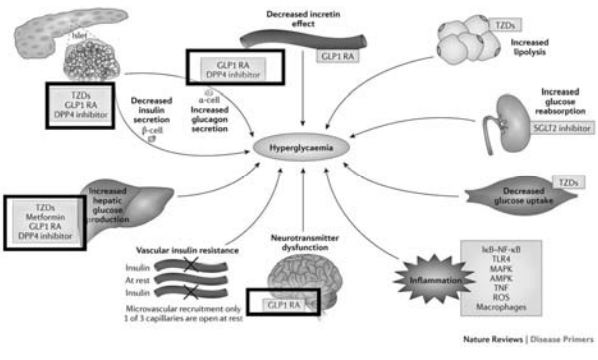
Neal B, et al. N Engl J Med. 2017;377:644-657.

Cardiovascular/Renal Outcomes

- In people with uncontrolled T2DM and established CV disease (or specifically to reduce CV risk), consider:
  - The oral **SGLT-2 inhibitors canagliflozin or empagliflozin**
  - The injectable **GLP-1 agonists liraglutide or semaglutide**
- These agents also showed beneficial effects on renal outcomes
  - progression to macroalbuminuria (>300 mg alb/g Cr), doubling of the serum creatinine level and eGFR of ≤45, initiation of renal-replacement therapy, death from renal disease

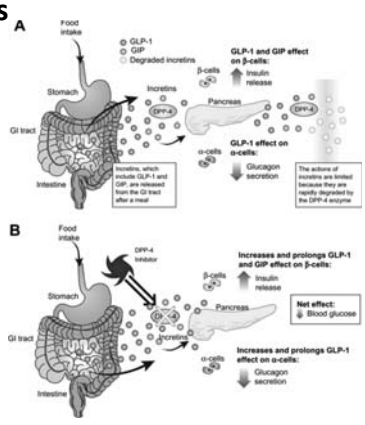
American Diabetes Association. Diabetes Care 2018;41:S86–S104.

Dipeptidyl peptidase-4 (DPP) Inhibitors



DeFronzo, R. A. *et al.* (2015) Type 2 diabetes mellitus
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.19

DPP4 Inhibitors



Core Evid. 2010 Oct 21;5:23-37.

DPP4 Inhibitors

- FDA-approved agents: sitagliptin, saxagliptin, linagliptin, alogliptin

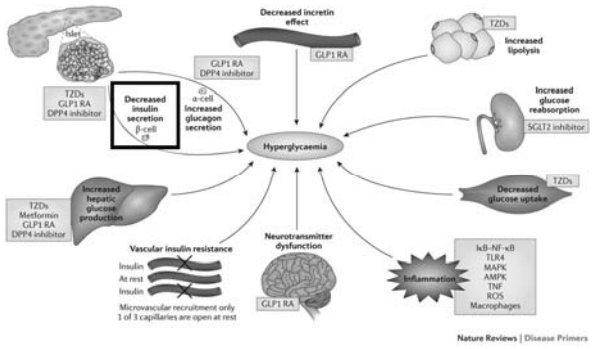
Benefits	Limitations
Oral	Modest A1c efficacy
No hypoglycemia	High cost
Well tolerated	
Can be used in CKD/ESRD (w/ dose adjustments)	

American Diabetes Association. Diabetes Care. 2018;41:S73-S85.
Heerspink HJ, et al. Circulation. 2016;134:752-772.

Less preferred oral medication for older adults:

1. Sulfonylureas
2. Thiazolidinediones

Sulfonylureas



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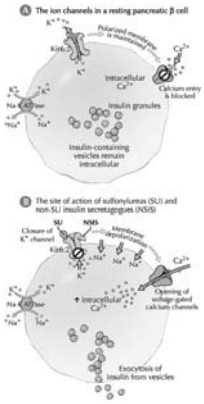
Sulfonylureas



Insulin secretagogues mimic glucose to close adenosine triphosphate-sensitive potassium channels (kir6.2) and stimulate insulin secretion.

Alice Y.Y. Cheng, and I. George Fantus CMAJ 2005;172:213-226

Sulfonylureas

- FDA-approved agents: glyburide, glipizide, glimepiride

Benefits	Limitations
▪ Cheap	▪ Hypoglycemia
▪ Extensive clinical experience	▪ Weight gain
▪ Oral	▪ Low durability
	▪ **Glyburide not recommended especially in older adults to to higher risk of hypoglycemia**

American Diabetes Association. Diabetes Care. 2018;41:S73-S85.
Heerspink HJ, et al. Circulation. 2016;134:752-772.

74-year-old man with T2DM admitted for hypoglycemia.

Home regimen: 20 units of degludec insulin BID, saxagliptin 5mg and glimepiride 2mg daily.

Two days ago, low blood glucose of 64 before so decreased degludec to 10 units that night. Next morning, CBG 60's again and skipped all of his insulin. He continued his saxagliptin and glimepiride the day before admission.

Patient was brought in by EMS this morning for hypoglycemia with CBG 40's and neuroglycopenic symptoms. He is 36 hours from his last dose of insulin and 24 hours from his last dose of saxagliptin and glimepiride. He has normal renal function at baseline, but noted on admission Cr=2.6.

1. Which of the following is contributing to this patient's persistent hypoglycemia?

a. Saxagliptin
b. Insulin
c. Glimepiride
d. Insulin & Glimepiride

1. Which of the following is contributing to this patient's persistent hypoglycemia?

a. Saxagliptin
b. Insulin
c. Glimepiride
d. Insulin & Glimepiride

- Degludec insulin falls into the ultra-long acting insulin class. The duration of action is 40+ hours.
- As GFR declines, active metabolites of glimepiride accumulate contributing to ongoing stimulation of endogenous insulin release

Why doesn't Saxagliptin cause hypoglycemia?

- DPP4 inhibitors inhibit breakdown of GLP1, GLP1 contributes to slowing carbohydrate absorption and improve glucose-stimulated insulin secretion.

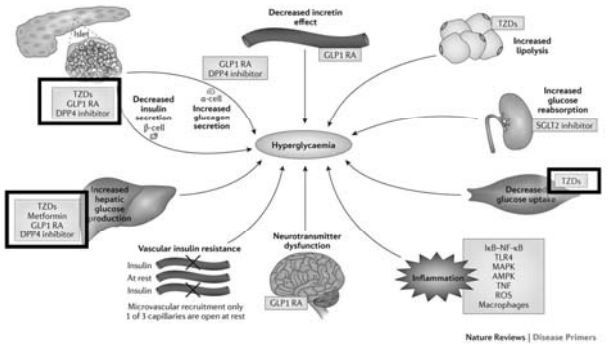
What is wrong with how he has been taking the degludec insulin?

- Ultra-long acting insulins (degludec (Tresiba) , glargine U300 (Toujeo) should only be administered once daily

When do we expect the degludec insulin to be out of his system?

- 5 half lives of ~25 hours -> 5 days from now

Thiazolidinediones (TZDs)



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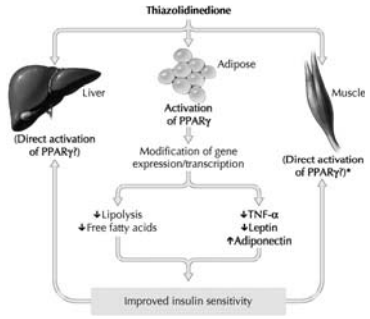
Thiazolidinediones (TZDs)



Alice Y.Y. Cheng, and I. George Fantus CMAJ 2005;172:213-226

Thiazolidinediones (TZDs)

- FDA-approved agents: pioglitazone, rosiglitazone

Benefits

- Oral
- No hypoglycemia
- Benefit in NASH
- Increased HDL, Decrease TGs

Limitations

- FDA Black Box warning for heart failure (fluid retention)
- Weight gain
- Increased risk of fractures
- Increased LDL (rosiglitazone)
- ?bladder cancer

American Diabetes Association. Diabetes Care. 2018;41:S73-S85.
Heerspink HJ, et al. Circulation. 2016;134:752-772.

Simplifying complex insulin regimens:

Basal Insulin:

1. Change timing from bedtime to morning
2. Titrate dose based on fasting glucose values over 1 week
   - Fasting goal 90-150mg/dl (may change based on goals of care)
3. If 50% of glucose values are above the goal -> increase by 2 units
4. If >2 values/week are <80 mg/dL -> decrease dose by 2 units

Mealtime Insulin:

1. If mealtime dose >10 units -> decrease by 50% and add non insulin agent
2. Titrate meal doses down as noninsulin agent increased with aim to discontinue mealtime insulin
3. If mealtime dose <10 units -> stop mealtime insulin and add non insulin agent

Premixed insulin:

1. Use 70% of dose as basal only in the morning

Adding noninsulin agents:

1. If eGFR >45, start metformin
2. If eGFR <45 or already on metformin proceed second-line agent

Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

Simplifying complex insulin regimens, continued…

- Do not use short-acting insulin at bedtime
- While adjusting mealtime insulin, may use simplified sliding scale:
  - Premeal >250 -> add 2 units of short-acting insulin
  - Premeal >350 -> add 4 units of short-acting insulin
- Stop sliding scale when not needed daily

Older Adults: Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42(Suppl. 1):S139–S147

69 yo man with T2DM, obesity, hypertension, hyperlipidemia, sleep apnea, PTSD. A1c is up to 10.4% (8-9 in last few years), weight is 258 (BMI 39), he has been trying very hard to work on diet and increase exercise and still his insulin requirements continue to increase (60 units -> 80 units glargine) along with his A1c. He also takes 2g metformin daily.

He wants to know what else he can do improve his weight and diabetes control. He really doesn't want to take insulin more than once a day.

1. **What should you ask him about how he is taking his glargine?**
   a. How often are you changing the pen needle?
   b. Are you taking 80 units as one shot?
   c. How often do you miss doses?
   d. All of the above

2. **What medication(s) could we add to his regimen?**
   a. GLP1 receptor agonist
   b. SGLT2 inhibitor
   c. DPP4 inhibitor
   d. Any of the above

1. **What should you ask him about how he is taking his glargine?**
   a. How often are you changing the pen needle?
   b. Are you taking 80 units as one shot?
   c. How often do you miss doses?
   d. All of the above

- Max dose for glargine in one shot 50-60 units, should take as 2 shots at same time or BID.
- Some evidence for less weight gain if take it all at once as two shots

2. What medication(s) could we add to his regimen?
- What contraindications should you ask about?
   a. GLP1 RA: Pancreatitis, Medullary thyroid cancer
   b. SGLT2 inhibitor: Kidney function, history of DKA, history of amputations
   c. DPP4 inhibitors: ?heart failure
   d. Any of the above

70 yo man with poorly controlled T2DM (last A1c 9.3%) on 40 units glargine daily, no other diabetes medications, prior admission for hyperosmotic hyperglycemic nonketotic state (HHNK), s/p unilateral nephrectomy for RCC, CKD stage 3 with last Cr 1.6 (GFR 50), hypothyroidism, history of lung carcinoid s/p resection.

He was started on liraglutide, but A1c and weight continued to go up over three months, despite maximum liraglutide dose.

1. **What do you do with the liraglutide?**
   a. Continue mediation for another 3-6 months to monitor for effect
   b. Increase dose above recommended maximum dose
   c. Stop liraglutide, patient is a non-responder

2. **What medication changes are indicated here?**
   a. Increase insulin doses by 20%
   b. Start low dose metformin
   c. Try another GLP1 RA
   d. Start SGLT2 inhibitor

3. What do you do with the liraglutide?
   a. Continue mediation for another 3-6 months to monitor for effect
   b. Increase dose above recommended maximum dose
   c. Stop liraglutide, patient is a non-responder

4. What medication changes are indicated here?
   a. Increase insulin doses by 20%
   b. Start low dose metformin
   c. Try another GLP1 RA
   d. Start SGLT2 inhibitor

- Low dose metformin (5000-1000mg daily) with BMP monitoring q3 months
- FDA now allows for initiation metformin down to GFR 45
- Can continue metformin down to GFR 30 with close monitoring

Continuous Glucose Monitoring

- CGM provides much more information than SMBG
  - Glucose value
  - Trend arrow
  - Rate of change
  - Trend graph
    - Know where you are by how you got there AND where its going

Abbott Freestyle Libre
- FDA approval September 2017
- Factory-calibrated
- 10-day wear
- Non-adjunctive (insulin-dosing) approval

Dexcom G6 CGM
- FDA approval March 2018
- Factory-calibration option
- 10-day wear
- Non-adjunctive (insulin-dosing) approval

Senseonics Eversene CGM
- FDA approval June 2018
- Implanted CGM sensor
- 90-day wear
- Approved for 180-day wear in EU

Evidence for CGM

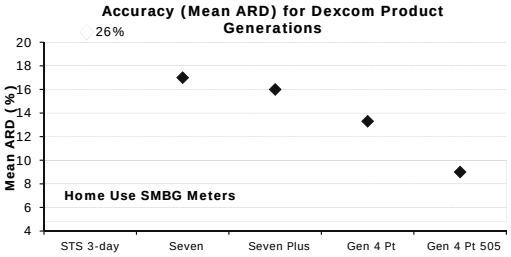
	CGM			Control			
	Baseline (n = 63)	12 weeks (n = 61)[a]	24 weeks (n = 58)[a]	Baseline (n = 53)	12 weeks (n = 52)[a]	24 weeks (n = 50)[a]	*P* value[b]
Mean glucose, mg/dL	175 ± 25	167 ± 27	168 ± 29	179 ± 30	178 ± 28	180 ± 28	.01
Glycemic variability, coefficient of variation %	34 (28, 42)	33 (28, 37)	31 (28, 36)	34 (29, 38)	33 (28, 38)	33 (27, 39)	.02
Time spent: 70-180 mg/dL, min/day	796 ± 236	892 ± 256	889 ± 251	753 ± 253	767 ± 265	732 ± 252	<.001
Time spent: >250 mg/dL, min/day	172 (83, 281)	93 (30, 180)	89 (37, 208)	208 (112, 294)	180 (81, 251)	179 (83, 316)	.006
Time spent: <60 mg/dL, min/day	10 (1, 38)	4 (0, 15)	3 (0, 15)	8 (1, 23)	4 (0, 27)	4 (0, 24)	.11

DIAMOND study:

- multicenter, randomized trial, n=116, ≥60 years old with T1D (n = 34) or T2D (n = 82) using MDI therapy assigned **Dexcom G4 CGM** or **continued SMBG**

Journal of Diabetes Science and Technology 2017, Vol. 11(6) 1138 –1146

Advances in accuracy



Advances in accuracy

Medicare coverage for CGM

- Type 1 or type 2 diabetes
- Home blood glucose monitoring >= 4 times/day
- 3 or more daily injections of insulin or insulin pump
- Treatment regimen requires frequent adjustments on basis of CGM values
- Visit with in 6 months prior to ordering CGM
- Follow up visits ever 6 months with assessment of CGM adherence and diabetes treatment plan

https://www.dexcom.com/faq/medicare

OHSU

The end.

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Oregon Health & Science University

February 14th, 2019
50th Annual Primary Care Review

Creating a Culture of Well-Being & Resiliency:
Strategies to Promote Engagement and Reduce Burnout

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Portland, Oregon

Disclosure Statement

- Potential conflicts of interest: none
- Sponsorship: none
- Presentation is educational in nature and indicates agreement to abide by the non-commercialism guidelines provided

Definitions

Burnout[1]: a syndrome characterized by a high degree of emotional exhaustion and depersonalization (i.e. cynicism) and a low sense of personal accomplishment at work

Engagement[2]: emotional commitment the employee has to the organization and its goals

Resiliency[3]: the ability to grow and thrive in the face of challenges and bounce back from adversity

Well-Being[4]: a positive outcome that is meaningful for people and for many sectors of society, because it tells us that people perceive their lives are going well

1. National Academy of Medicine. Clinician Well-Being Knowledge Hub. https://nam.edu/clinicianwellbeing/about/ (accessed 2018 Nov 14)
2. Forbes. 14 Employee Well-Being Initiatives That Will Boost Engagement And Productivity. (accessed 2018 Nov 14)
3. Jefferson CC. Building Resilience Across USARPAC. *United States Army*. 2011
4. Centers for Disease Control and Prevention. Well-Being Concepts. https://www.cdc.gov/hrqol/wellbeing.htm (accessed 2018 Nov 14)

Objectives

- Discuss the complexity between burnout & depression and well-being & resiliency
- Describe factors that affect well-being & resiliency
- Identify ways to promote well-being and resiliency in a complex healthcare environment

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- Discuss the complexity between burnout & depression and well-being & resiliency
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Burnout: Definitions

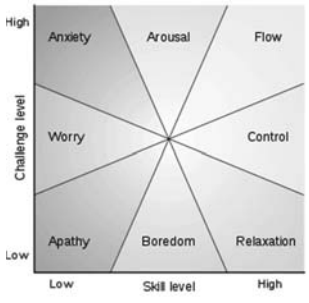
- Emotional depletion: feeling frustrated, tired of going to work, hard to deal with others at work
- Detachment/cynicism: being less empathetic with patients/others, detached from work, seeing patients as diagnoses/objects/sources of frustration
- Low personal achievement: experiencing work as unrewarding, "going through the motions"
- Depersonalization: thoughts and feelings seem unreal or not belonging to oneself

Drivers of Burnout

- Excess stress mediated by long hours, fatigue and work compression as well as the intensity of work environment
- Loss of meaning in medicine and patient care:
  Decreased support, increased responsibility, without autonomy and flexibility
- Challenges in institutional cultures: perceived lack of peer support, lack of professionalism, disengaged leadership
- Problems with work-life balance

Poor Stress Response → Burnout

Challenge vs. Skill Level



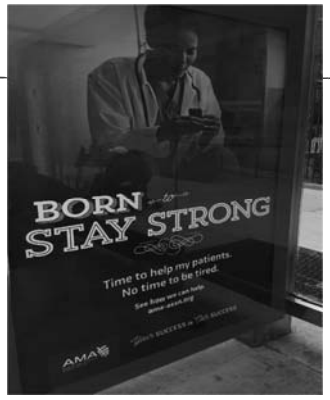
Risk Factors for Burnout

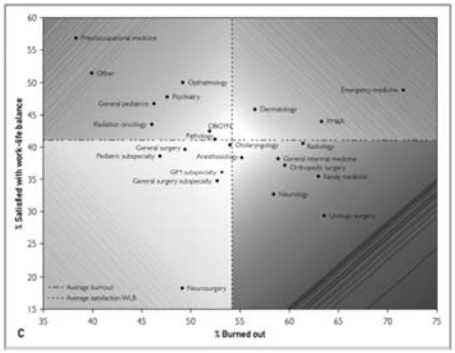
- Sleep deprivation
- High level of work/life conflict
- Work interrupted by personal concerns
- High level of anger, loneliness, or anxiety
- Stress of work relationships
- Anxiety about competency
- Difficulty "unplugging" after work
- Regular use of alcohol and other drugs

Burnout Among Health Care Professionals

- More than half of US physicians are experiencing substantial symptoms of burnout
- Burnout is nearly twice as prevalent amount physicians as US workers in other fields
- Studies of nurses and other health care professionals report similarly high prevalence of burnout and depression

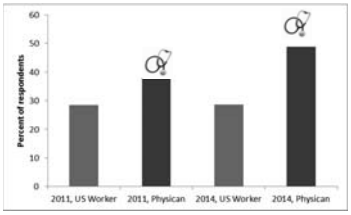
West, CP et al, JAMA 2006; Desai et al, JAMA 2013; Sen S, JAMA Intern Med 2013

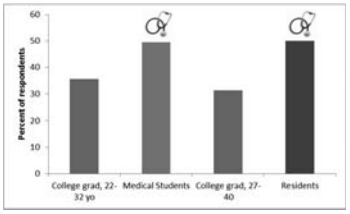




Shanafelt et al Mayo Clin Proc 2015

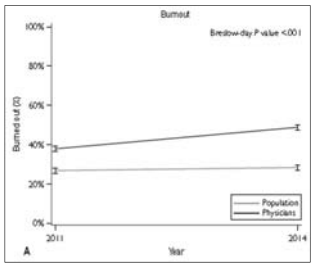
Prevalence of Burnout

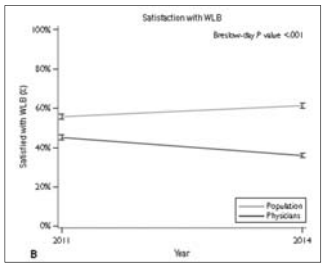




Aiken JAMA 2002;288; McHugh Health Aff 2011;30; Dyrbye Acad Med 89(3)

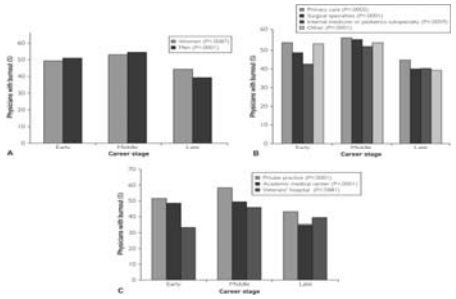
Burnout and Work-Life Balance





Shanafelt, et al., Mayo Clinic Proceedings, December 2015

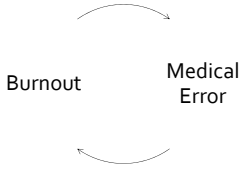
Burnout at Career Stage



Dyrbye et al. Mayo Clinic Proc, 2013

Quality and Safety Implications

- Increase in Patient Safety Incident (PSI) reports
- Increase in mortality ratios
- Healthcare associated infections
- Medical malpractice



Shanafelt TD et al. JAMA Int Med. 2017
Aiken JAMA 2002;288; McHugh Health Aff 2011;30; Dyrbye Acad Med 89(3)

Financial Implications

↑Medical errors

↑Malpractice claims

↑Job turnover

↑Absenteeism

↓Productivity

Jones J Nurs Am 2008; Fibuch Physician Leadersh J 2015; Buchbinder Am J Manag Care 1999, Kushnir, Fam Pract 2014; Bachman Soc Sci Med 1999; Parker J Behav Med 1995; Toppinen-Tanner Behav Med 2005, Hilton J Occup Environ Med 2009

The Business Case for Well-Being

- Costs Associated with Turnover
  - Burnout is a major driver of physician turnover
  - Cost to replace a physician is 2-3 times the physicians annual salary
  - Mean cost of replacing a physician=$500,000 to $1,000,000.
- Costs associated with decreased productivity
- Financial risk to organizations long term viability
  - Relationship between physician burnout and quality of care, patient safety and patient satisfaction

Shanafelt TD et al. JAMA Int Med. 2017

Burnout, Depression and Suicide

	Medical Student	Resident	Early Career < 5yr
Burnout	56%	51%	40%
Depression*	58%	51%	40%
Suicidal Ideation (last 12 months)	9.4%	8.1%	6.3%

* - Depression screen using 2-item PRIME MD

Dyrbye, Acad Med. 2014;89(3):443

Depression – DSM5

- 5 or more of the following symptoms for ≥2 weeks:
  - Depressed mood most of the day
  - Diminished interest or pleasure
  - Significant weight loss or gain
  - Insomnia or hypersomnia nearly every day
  - Psychomotor agitation or retardation
  - Fatigue of loss of energy
  - Feelings of worthlessness or excessive guilt
  - Diminished ability to concentrate
  - Recurrent thoughts of death or suicidal ideation with or without a plan

APA, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

Depression During Medical Internship

- Rate of depression increased dramatically during internship from 3.9% meeting PHQ-9 criteria (scores ≥10) up to 25.3% at intervals during the year
- Mean PHQ-9 increased from 2.4 to 6.4
- Depression results in increased medical errors and errors may also cause depression
- Direct association between the number of hours worked and the risk of depression
- No evidence that depressive symptom score before internship predicted an increase in work hours

Sen et al. Arch Gen Psych, 2010

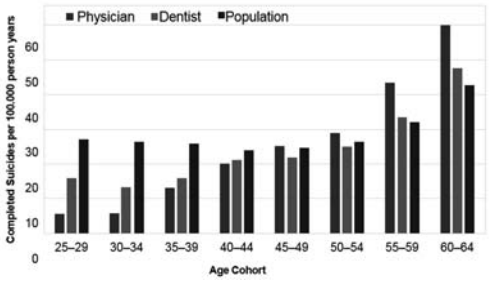
Predictors of Depressive Symptoms

Baseline Factors
- Neuroticism
- Personal history of depression
- Lower baseline depressive symptoms
- Female sex
- US medical graduate
- Difficult early family environment
- 5-HTTLPR polymorphism

Within-Internship Factors
- Higher mean work hours
- Perceived medical errors
- Stressful life events

Sen et al. Arch Gen Psych, 2010

Incidence of Suicide



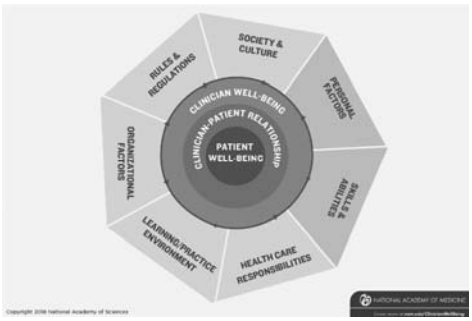
Occup Med (Lond). 2008 58 (1): 25-29.

Objectives

- Discuss the complexity between burnout & depression and well-being & resiliency
- Describe factors that affect well-being & resiliency
- Identify methods to promote well-being and resiliency in a complex healthcare environment

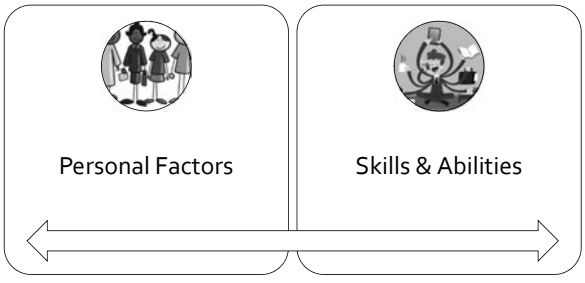
National Academy of Medicine

Factors Affecting Clinician Well-Being and Resilience



External Factors

Individual Factors



Objectives

- Discuss the complexity between burnout & depression and well-being & resiliency
- Describe factors that affect well-being & resiliency
- Identify methods to promote well-being and resiliency in a complex healthcare environment

Resiliency

- The ability to grow and thrive in the face of challenges nd bounce back from adversity
- The capacity to bounce back, to withstand hardship, and to repair yourself
- Positive adaptation in the face of stress or disruptive change
- Based on a combination of factors:
  - Internal attributes (genetics, optimism)
  - External (modeling, trauma)
  - Skills (problem solving, finding meaning/purpose, practicing mindfulness)

Jefferson CC. Building Resilience Across USARPAC. United States Army. 2011
Wolin 1993, Werner & Smith, 1992

Br J Gen Pract. 2016 Jul;66(648):e507-15

Strategies to Increase Resilience

- Realistic recognition (Overcoming denial/culture)
- Exercise, sleep, nutrition
- Supportive professional relationships
- Boundaries
- Time away from work
- Passion for one's work
- Hobbies outside medicine
- Humor
- Supportive personal relationships
- Practicing mindfulness
- Focusing on positive emotions like gratitude and optimism

Well-Being Interventions

1. **Educate and Increase Awareness**
   - Using these slides!
   - Create a Speaker's Bureau
2. **Designate Time for Reflection**
   - Groups, debrief protocols
3. **Teach Practical Skills**
   - Mindfulness, CBT, exercise
4. **Build Community**
   - Diversity
   - Mentoring and coaching programs
   - Opportunities to socialize at work
5. **Ensure Access to Care**
   - Confidential, easy to access, available both during and after work hours
   - 24-hour emergency phone line
   - Online resources with screening tools for burnout, depression and suicide
6. **Improve Workplace Environment**
   - Review workloads and schedules with physician input, autonomy, flexibility
   - Adequate staffing to reduce admin/clerical tasks for physicians
   - Personnel optimized to work at top of licenses in most meaningful work
7. **Transform Institutional Culture**

Developed by ML Goldman, CA Bernstein, LS Mayer

Educate and Increase Awareness

- Offer educational opportunities about:
  - Burnout, depression, substance abuse, suicide, and stigma
  - Epidemiology of psychiatric illness and comorbidity
  - Effectiveness of treatment options for depression and other mental illnesses
  - Sleep hygiene, nutrition, gyms, housing, fun activities
  - Both mental and physical health resources
- High-yield venues include:
  - Orientation sessions for incoming trainees or employees
  - Departmental grand rounds
  - Didactic sessions either in training curricula or Graduate Medical Education (GME) and Continuing Medical Education (CME) settings

Developed by ML Goldman, CA Bernstein, LS Mayer

Designate Time for Reflection

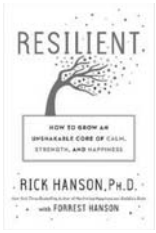
- 12 studies involved individual-focused interventions
- Interventions included
  - Facilitated small group curricula
  - Stress management and self-care training
  - Communication skills training

- Four of these studies indicated funding or coverage for physicians to participate during the workday

West, et al., Lancet, November, 2016

Teach Practical Skills

- Mindfulness-based stress reduction techniques
- Stress awareness and cognitive-behavioral techniques
- Positive psychology/emotional intelligence
- Physical exercise groups



Developed by ML Goldman, CA Bernstein, LS Mayer

Build Community

- Expand structured mentorship and professional development programs
- Recurring social events and shared community resources
- Department led team-building activities and funded annual retreats

Developed by ML Goldman, CA Bernstein, LS Mayer

Ensure Access to Care

- Screen for burnout and depression
- Define a clear system for referrals to individual mental health services
- Provide in-house mental health services for physicians
- Develop well-being center
- Arrange after-hours emergency phone line

Developed by ML Goldman, CA Bernstein, LS Mayer

Improve Workplace Environment

- Involve staff in Quality Improvement to address workflow issues including:
  - Health information technology updates to improve user experience
  - Physical infrastructure with shared spaces conducive to collaboration and team building
  - Personnel optimized to work at top of licenses (e.g. task shifting, delegating)
  - Physicians given autonomy to spend at least 20% of day in most meaningful work
- Hold regular meetings with leadership to improve work environment with follow-up
- Develop a comprehensive strategic plan with operations management to address workforce issues and barriers

Developed by ML Goldman, CA Bernstein, LS Mayer

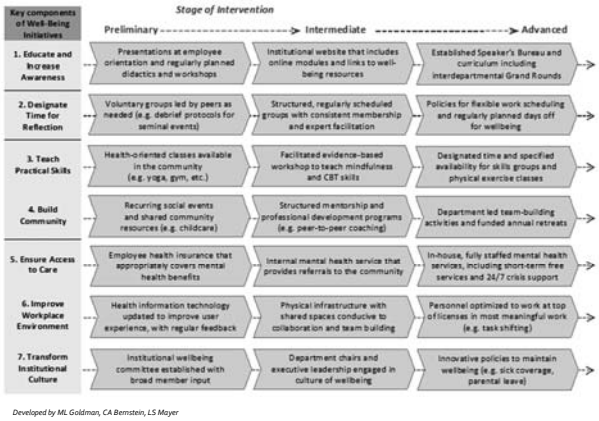
Transform Institutional Culture

- Encourage department chairs and executives to engage in participatory leadership styles to facilitate a culture of wellbeing
- Promote clear and standardized policies for taking personal days to care for self, sick coverage, and parental leave
- Establish an institutional Well-Being Committee with broad member input
- Participate in existing and innovative research studies
- Assess adherence to regulatory guidelines and requirements

Developed by ML Goldman, CA Bernstein, LS Mayer

6 Step Plan to Well-Being

1. Get Organized
2. Assess Your Needs
3. Choose Your Priorities
4. Engage Leadership
5. Stay Accountable
6. Anticipate Obstacles



Developed by ML Goldman, CA Bernstein, LS Mayer

Key Points

- ❖Clinician burnout affects all interdisciplinary healthcare workers that can be alleviated by individual and organizational focused interventions
- ❖Long-term professional and personal growth of employees must be a core value for all leaders practicing in healthcare
- ❖Resiliency, wellness, and work-place effectiveness can lead to a more engaged and rewarding healthcare environment

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Penicillin Allergy, Anaphylaxis, and Other Updates in Drug Allergy

Primary Care Review – February 14th, 2019
Shyam Joshi, MD
Assistant Professor of Medicine
Section of Allergy and Immunology

Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- Understand the varied clinical presentations seen with drug allergies
- Review the clinical data on clinical decision making in patients with drug allergies
- Be able to identify which patients should have further evaluation after a drug-related adverse event

Presentation Outline

- Case Presentation
  - Defining drug allergies
  - Importance of questioning drug allergies
  - Myths in drug allergy
- Penicillin Allergies
  - Proactive approach to testing
- Future of drug allergy testing

Case Presentation

RJ is a 70 year-old gentleman with a history of asthma, food allergy (egg- and shellfish-associated anaphylaxis) that was admitted for pneumonia. Presents on the floor with this rash along with nausea, vomiting and progressive nonproductive cough.

How Common Are Adverse Drug Events?

Allergy Label

- 36% of patients have a listed allergy in their EMR
  - 43% of these had multiple allergies
  - 4-7% have MDIS
- Risk factor: Drug exposure

Adverse Events

- Adverse drug events occur in up to 25% of prescriptions
  - 13% of these were serious
- Allergic reactions (immunologically mediated) account for only 5-10% of all ADEs

Zhou L et al. *Allergy,* 2016.
Gandhi TK et al. *NEJM*, 2003.

Classifying Adverse Drug Events

Type A Reactions

- Predictable – Due to known pharmacodynamics of the drug (dose-dependent)
- Based more on drug than host
- >85% of ADEs
- Examples
  - Sedation with diphenhydramine
  - Diarrhea with amoxicillin
  - Bleeding due to warfarin

Type B Reactions

- Unpredictable
- Based more on host than drug
- ~15% of ADEs
- Examples
  - Hypersensitivity reactions
  - Pseudoallergies

Drug Allergy Classification

Gell-Coombs Classification	
Type I	IgE-mediated
Type II	Cytotoxic
Type III	Immune-mediated
Type IV	Delayed-type
Type IVa	Monocytes/eczematous
Type IVb	Eosinophils/eczematous
Type IVc	Cytotoxic T cells/bullous
Type IVd	Neutrophils/pustular

Biologics Allergy Classification

Table 2
Proposed classification of adverse reactions to biologic agents

Type	Example Reaction (Causative Medication)
α: Overstimulation	Cytokine release syndrome (cytokine storm) (muromunab, TGN1412)
β: Hypersensitivity	Common acute infusion reactions (rituximab), delayed infusion reactions (etanercept, adalimumab), anaphylaxis (muromunab, cetuximab, omalizumab)
γ: Cytokine or immune imbalance	
Immunodeficiency	Increased risk of tuberculosis (anti-TNF agents) Hypogammaglobulinemia (rituximab)
Autoimmunity	Systemic lupus erythematosus or vasculitis (IFN-γ)
Atopic disorders	Atopic dermatitis (anti-TNF agents)
δ: Cross-reactivity	Acne from anti-EGFR (cetuximab)
ε: Nonimmunologic side effects	Neuropsychiatric side effects including confusion or depression (IFN-α)

Patel SV and Khan DA. *Immunol Allergy Clin N Am*, 2017.

Case Presentation

- In the past 24 hours, he has received the following:
  - Outpatient infusion: Omalizumab (2nd dose)
  - Outpatient vaccination: Influenza vaccine
  - Emergency room:
    - IV Contrast – CTA chest to evaluate for a PE
    - Vancomycin/Pip/Tazo (pneumonia/sepsis)

Myths & Truths

Myth #1: All drug allergies are equal and management should be the same regardless of the reaction. The only solution is drug avoidance.

Truth #1: Each drug allergy is unique and management should be determined on a case-by-case basis. Avoidance is not the only management solution.

Variety of Drug Allergies

Examples of Drug Allergies		
IgE-mediated	Pneumonitis	Urticaria multiforme
Hemolytic anemia	AIN	Erythema multiforme
Thrombocytopenia	Drug-induced lupus	AGEP
Granulocytopenia	FDE	Infusion reactions
Serum sickness	Contact dermatitis	Atopic dermatitis
Serum sickness-like	Acne	Angioedema
Vasculitis	Photosensitivity	IgE-mediated anaphylaxis
Arthus reaction	SDRIFE	Non-IgE-mediated anaphylaxis
DRESS	Drug exanthema	IgG-mediated anaphylaxis
SJS	Drug fever	MRGPRX2-mediated
TEN	Bullous pemphigoid	Pemphigus vulgaris

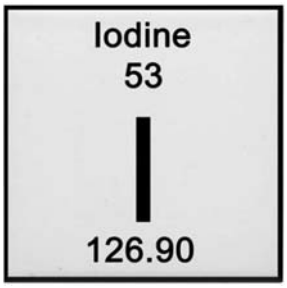
Myths & Truths

Myth #2: Patients with a shellfish allergy should avoid IV contrast.

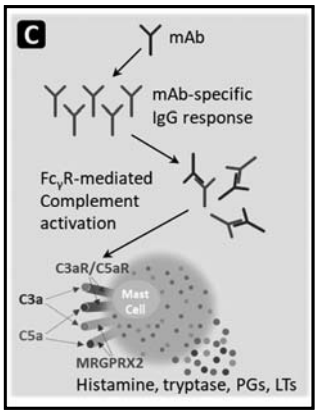
Truth #2: No association between shellfish allergy and contrast allergy.

Contrast Pseudoallergy

- Iodine is NOT an allergen
- Shellfish allergy is due to specific proteins (tropomyosin) which are not found in contrast
- Risk of reaction to contrast (in a shellfish allergic patient) is the same as any atopic individual



Contrast Anaphylactoid Reaction



- Mas-Related G-Protein Coupled Receptor Member X2 (MRGPRX2)
- Vancomycin, ciprofloxacin, cisatracurium, and opiates
  - First-dose anaphylaxis
- May play a role in ionized contrast media (ICM) reactions

McNeil BD, et al. *Nature*, 2015.
Navines-Ferrer A, et al. *Sci Rep*, 2018.

Myths & Truths

Myth #3: If you have a egg allergy/intolerance, you should not receive Propofol or the Influenza Vaccine.

Truth #3: Reaction rates to Propofol or the Influenza Vaccine are similar between egg-allergic and non-egg allergic individuals.

Influenza Vaccine and Egg Allergy

- Influenza vaccines are grown in embryonated chicken eggs
  - May contain trace egg protein (ovalbumin)
  - Ovalbumin content = 1µg per dose (unlikely to cause reaction)
- 2 large prospective multi-center trials showed no increased risk in egg allergic patients
- "Special precautions for egg-allergic recipients of IIV are not warranted, because the rate of anaphylaxis after IIV administration is no greater in egg-allergic than in non–egg-allergic recipients or from other universally recommended vaccines."

Turner, et al. *BMJ*, 2015.
Turner, et al. *JACI*, 2015.

Myths & Truths

Myth #4: If your mother or father had a Penicillin Allergy, then you should avoid it too because you are at high risk for a severe reaction.

Myth #5: If you have had a reaction to Penicillin when you were a child, you are still allergic.

Truth #4: Drug allergies are not hereditary.

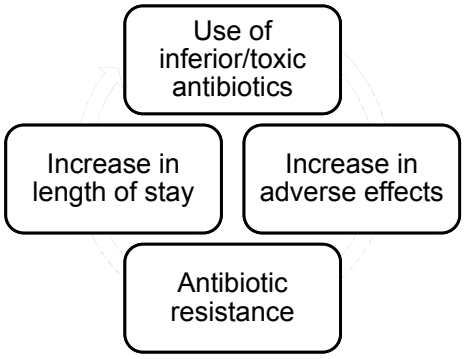
Truth #5: Penicillin sensitivity decreases over time.

Penicillin Allergy

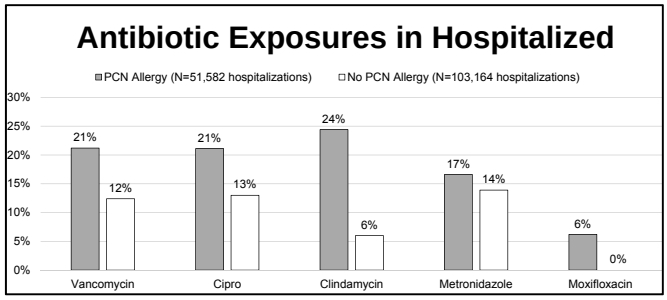
- 8-10% of the US population carries a history of penicillin allergy
  - >95% will tolerate penicillin use after evaluation
- Waning sensitivity to penicillin
  - 50% lose sensitivity by 5 years
  - 80% lose sensitivity by 10 years
- Subsequent penicillin use after negative testing does not increase risk of sensitization

Sogn DD, Evans R, Shepherd GM, et al. *Ann Intern Med*. 1992.
Gadde J, Spence M, Wheeler B, et.al. *JAMA*. 1993.
Macy E, Contreras R. *J Allergy Clin Immunol.* 2014.
Solensky R, Earl HS, Gruchalla, RS. *Arch Intern Med*, 2002.
Dorman SM, Seth S, Khan DA. *J Allergy Clin Immunol Pract*, 2018.

Effects of Penicillin Allergy Label



Antibiotic Exposure



Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.

Outcomes: PCN Allergy Label

1. Higher rate of treatment failures
2. Increased prevalence of Clostridium difficile, MRSA, and VRE
3. Increased future healthcare utilization
4. Increased healthcare dollars
5. Higher rates of surgical site infections

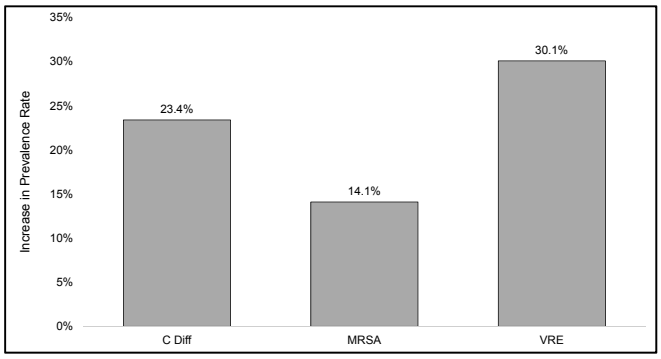
Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.
Jeffres MD, et al. *J Allergy Clin Immunol,* 2016.
Picard M, et al. *J Allergy Clin Immunol Pract,* 2013.
Blumenthal KG, et al. *Clin Infectious Dis*, 2018.

Treatment Failure

- The use of alternative antibiotics often results in higher rates of treatment failure
  - Jeffres et al. Treatment of GNB bacteremia
    - Non-β-lactam failure rate: 39%
    - β-lactam failure rate: 27%
  - McDanel et al. Treatment of MSSA bloodstream infections
    - β-lactams had a 35% lower mortality rate for definitive treatment compared to vancomycin

Jeffres MD, et al. *J Allergy Clin Immunol,* 2016.
McDanel JS, et al. *Clin Infect Dis,* 2015.

C diff, MRSA and VRE



Macy E, Contreras R. *J Allergy Clin Immunol*, 2014.
Reddy V, Baman NS, Whitener C, Ishmael FT, *J Allergy Clin Immunol,* 2013.

Future Healthcare Utilization

- Matched cohort
  - 308 patients that underwent testing
  - 1251 controls
- Tested group
  - Increased use of penicillins and 1st & 2nd generation cephalosporins
  - Decreased use of vancomycin, clindamycin, and macrolides
  - Fewer outpatient visits and few hospital days per year

Macy E, Shu YH. *JACI-In Practice*, 2017.

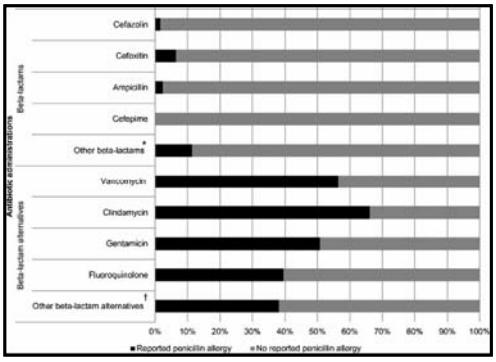
Increased Healthcare Dollars

Study	Findings
Jones and Bland (2017)	$315/patient in antibiotic costs
Estep et al. (2016)	$414/patient by switching from aztreonam
Heil et al. (2016)	$289/patient by switching from aztreonam
King et al. (2016)	$279/patient in antibiotic costs
Staicu et al. (2016)	$131-218/patient in antibiotic costs
Picard et al. (2013)	$91/patient in antibiotic costs

Does not include the costs savings as the result of treatment failure, increased hospitals stays, higher rate of rehospitalization, and long-term antibiotic use.

Picard M, et al. *J Allergy Clin Immunol Pract,* 2013.

Surgical Site Infections



When controlled for surgery type, age, sex, race, American Society of Anesthesiologists class, procedure duration, and wound class

⇩

51% increased risk of a SSI in patients that have a PCN allergy label (p<0.04)

Blumenthal KG, et al. *Clin Infectious Dis*, 2018.

Choosing Wisely Campaign (2014)

Choosing Wisely®
An initiative of the ABIM Foundation

American Academy of Allergy, Asthma & Immunology
American Academy of Allergy Asthma & Immunology
www.aaaai.org

Five Things Physicians and Patients Should Question

10 **Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation.**

https://www.choosingwisely.org

Penicillin Testing

- Modified protocol
  - Skin prick and intradermal testing
    - Penicilloyl-polylysine
    - Penicillin G
  - Observed (graded) oral amoxicillin challenge
- NPV of 97-100%
  - PPV not well established

https://www.medscape.com/viewarticle/871833

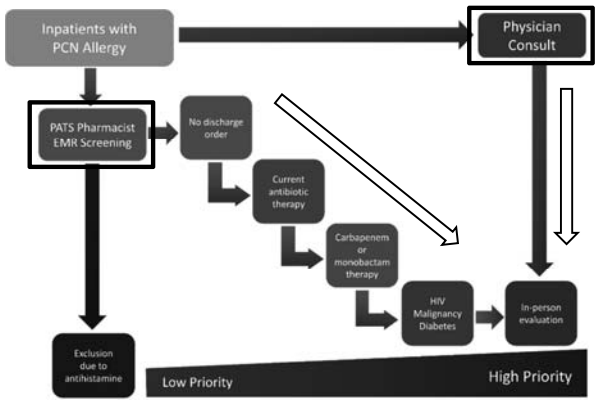
Clinical Approach to Penicillin Allergy

Inpatient vs. Outpatient Testing

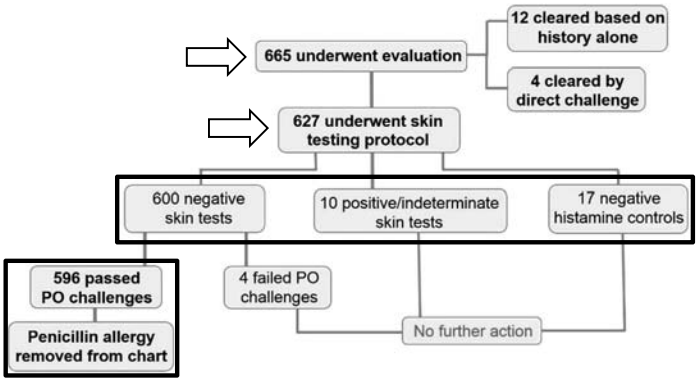
- Traditionally, penicillin skin testing has occurred in the outpatient setting
- Hospitalized patients:
  - Incidence of penicillin allergy is higher (up to 15%)
  - Older, more ill and greater need for antibiotics
  - Testing could alter antibiotic therapy immediately
- Outpatient:
  - Can perform multiple tests simultaneously
  - Difficult to schedule testing

Parkland Inpatient Allergy Testing

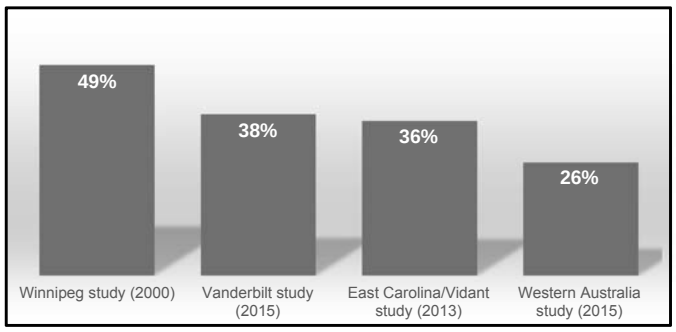
Inpatient Testing Protocol



Penicillin Testing Results



Penicillin Relabel

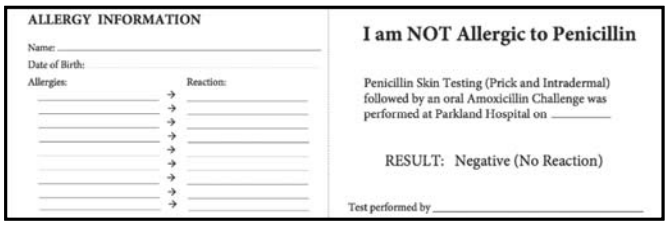


Warrington RJ, Lee KR, McPhillips S. *Allergy Asthma Proc.* 2000;21(5):297-9.
Gerace KS, Phillips E. *J Allergy Clin Immunol Pract.* 2015;3(5):815-816.
Rimawi RH, Shah KB, Cook PP. *Journal of Hospital Medicine.* 2013;8:615–618.
Bourke J, Pavlos R, James I, et. al. *J Allergy Clin Immunol Pract.* 2015;3:365-74.

Maintaining Penicillin Allergy Label Removal

1. Pharmacist counseling at the time of negative test
   - Active removal of allergy, procedure note documentation
2. Pharmacist counseling at post-discharge visit
   - Telephone call or face to face visit
3. Best practice advisory in the electronic medical record
   - Alerting providers to the negative penicillin allergy test result on attempt to add back allergy
4. Wallet card given to patient documenting negative testing
   - Given at time of negative test documentation

Wallet Card for Patient


ALLERGY INFORMATION

Name: _____

Date of Birth: _____

Allergies: Reaction:

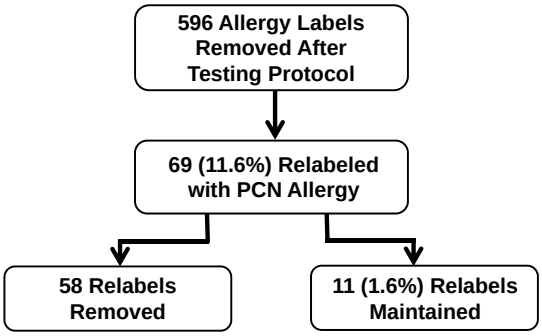
I am NOT Allergic to Penicillin

Penicillin Skin Testing (Prick and Intradermal) followed by an oral Amoxicillin Challenge was performed at Parkland Hospital on _____

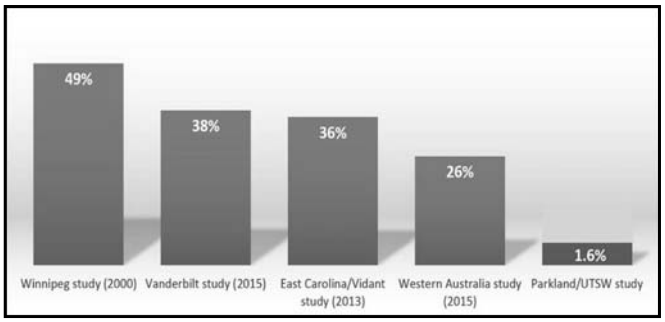
RESULT: Negative (No Reaction)

Test performed by _____

Relabel Study Results



Penicillin Relabel



Warrington RJ, Lee KR, McPhillips S. *Allergy Asthma Proc.* 2000;21(5):297-9.
Gerace KS, Phillips E. *J Allergy Clin Immunol Pract.* 2015;3(5):815-816.
Rimawi RH, Shah KB, Cook PP. *Journal of Hospital Medicine.* 2013;8:615–618.
Bourke J, Pavlos R, James I, et. al. *J Allergy Clin Immunol Pract.* 2015;3:365-74.

Case Presentation

- Treated with IM epinephrine with improvement of cutaneous, respiratory and GI symptoms
- Completed course of Moxifloxacin for pneumonia
  - Discharged home after 4 days in the hospital
  - 6 new allergy labels were added to his chart

Case Presentation

- Omalizumab: Possible (delayed IgE-mediated)
- Influenza vaccine: Possible/unlikely (no increased risk though)
- IV Contrast: Possible (no increased risk though)
- Vancomycin/Pip/Tazo: Possible

Each should be evaluated in the outpatient setting after the acute presentation resolves.

Case Presentation - Results

- Omalizumab: Tolerated next dose without problem.
- Influenza vaccine: Passed skin prick and intradermal. testing. Able to tolerate repeat influenza vaccine.
- Piperacillin/Tazobactam: Negative testing and passed challenge. Not allergic.
- Vancomycin: Negative testing but can have non-IgE-mediated allergy. Will need graded challenge if required in the future.
- Contrast: Most likely culprit and recommended pretreatment regimen if requires contrast again in the future.

Take Home Points

- Not all drug allergies are the same
- Questioning patients on their drug allergies can provide better outcomes for our patients
- Drug allergies are commonly reported – not frequently confirmed
  - Many patients can actually tolerate the medication in question
  - Patient education is key to prevent false allergy labels

Future of Drug Allergies

- Validated testing for drug allergies (other than PCN)
- Understanding non-IgE-mediated anaphylactic reactions
  - Role of platelet activating factor (PAF)
  - How MRGPRX2 plays a role
- Developing and analyzing the effectiveness of proactive drug allergy testing
  - Inpatient and outpatient

Acknowledgements

- University of Texas Southwestern Allergy/Immunology
  - Dr. Rebecca Gruchalla
  - Dr. David Khan
  - Dr. Shazia Lutfeali
  - Dr. Sheenal Patel
  - Kristin Alvarez, PharmD
  - Felecia Kasra, PharmD

Questions?

OHSU

Clinic for Asthma & Allergic Diseases

OHSU

Combined Clinic for Severe Sinus Disease

ENT & Allergy