PROGRAM
CTS MARCH 2022 CONFERENCE

Saturday, March 12, 2022

UPDATE ON SLEEP DISORDERS

7:00 am – 8:00 am
Registration & Breakfast

8:00 am – 8:15 am
Welcome and Pre-Test
Gaurav Singh, MD, MPH and Kristina Kudelko, MD

8:15 am – 9:05 am
Sleep Testing and Models of Care in the Post-COVID-19 Era
Kathleen Sarmiento, MD, MPH
Keynote Speaker

9:05 am – 9:50 am
Alternatives to Positive Airway Pressure Therapy for Sleep Disordered Breathing
Robson Capasso, MD

9:50 am – 10:35 am
Advances in Pharmacotherapy for Disorders of Hypersomnia
Gaurav Singh, MD, MPH

10:35 am – 10:50 am
Break

10:50 am – 11:35 am
Insomnia Management Strategies
Michelle Primeau, MD

11:35 am – 12:20 pm
Restless Legs Syndrome Management
Rafael Zuzuarregui, MD

12:20 pm – 1:20 pm
Lunch

1:20 pm – 2:20 pm
Hands-On Sessions: Hypoglossal Nerve Stimulator for OSA, Neuromuscular Electrical Stimulation and Positional Sleep Therapy for OSA, Forehead Cooling for Insomnia and Actigraphy, Medical Devices for Restless Legs Syndrome
Gaurav Singh, MD, MPH; Brandon Nokes, MD; Michelle Cao, DO; Michelle Primeau, MD; Rafael Zuzuarregui, MD

CLIMATE CHANGE AND ENVIRONMENTAL POLLUTION

2:20 pm – 3:05 pm
Wildfires and Effects on Obstructive Airways Diseases
Neeta Thakur, MD

3:05 pm – 3:50 pm
Climate Crisis: Impact on Lung and Overall Health
Jose Vempilly, MD

3:50 pm – 4:35 pm
Vaping: COVID-19 and More
Laura Crotty Alexander, MD

4:35 pm – 4:45 pm
Post-Test and Adjourn
Gaurav Singh, MD, MPH and Kristina Kudelko, MD

5:00 pm – 6:00 pm
Pandemic Career Development and Wellness Panel (NON-CME)
Moderators: Gaurav Singh, MD, MPH and Kristina Kudelko, MD
Panelists: Michelle Moore, MD; Susan Murin, MD, MSc, MBA; Mark Nicolls, MD; Dean Sheppard, MD
Available to view live via Zoom link for non-attendees

6:30 pm – 8:00 pm
Women In Pulmonary, Critical Care, and Sleep Medicine (NON-CME)
Moderator: Angela Wang, MD

SUNDAY, MARCH 13, 2022

8:00 am – 9:00 am
NON-CME BREAKFAST PRESENTATION

CALIFORNIA THORACIC SOCIETY

ANNUAL EDUCATIONAL CONFERENCE

Saturday, March 12, 2022

UPDATE ON SLEEP DISORDERS; CLIMATE CHANGE AND ENVIRONMENTAL POLLUTION

REGISTRATION & BREAKFAST

7:00 a.m. – 8:00 a.m.

WELCOME AND PRE-TEST

8:00 a.m. – 8:15 a.m.

KRISTINA KUDELKO, MD
STANFORD UNIVERSITY

Dr. Kristina Kudelko is a Clinical Associate Professor in the Division of Pulmonary, Allergy, and Critical Care Medicine at Stanford University. Dr. Kudelko sub-specializes in pulmonary hypertension in which she completed an advanced fellowship in 2009. She is highly invested in teaching, mentorship, and wellness. She is the Program Director for the eBay fellowship in pulmonary vascular disease at Stanford and the Director of Education and Steering Committee member of the Vera Moulton Wall Center for Pulmonary Vascular Disease.

GAURAV SINGH, MD, MPH
VA PALO ALTO HEALTH CARE SYSTEM
STANFORD UNIVERSITY

Dr. Gaurav Singh received his medical degree from UCSF and completed a Masters of Public Health at UC Berkeley. Currently, he is a Staff Physician at the VA Palo Alto Health Care System in the Section of Pulmonary, Critical Care, and Sleep Medicine. He is also an Affiliated Clinical Assistant Professor at Stanford University, where he completed training in Internal Medicine, followed by Pulmonary and Critical Care fellowship as well as Sleep Medicine fellowship. Dr. Singh has been involved with CTS since 2018 and has been a speaker for the Northern California Annual Conferences in 2019 and 2020. He served on the planning committee for the cancelled CTS Northern California Annual Conference in 2021. He is Conference Co-Chair for the 2022 CTS Annual Educational Conference.

Sleep Testing and Models of Care in the Post-COVID-19 Era

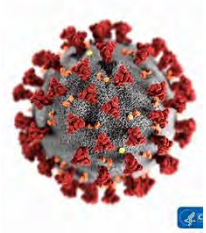
8:15 a.m. – 9:50 a.m.

KATHLEEN SARMIENTO, MD, MPH
SAN FRANCISCO VA HEALTH CARE SYSTEM
UC SAN FRANCISCO
KEYNOTE SPEAKER

Dr. Kathleen Sarmiento is a Professor of Medicine at UC San Francisco and the executive director for VA's National Sleep Medicine Program. Her interests and expertise are in program development, health services research and implementation of strategies that improve access, reduce disparities, lower cost, and eliminate low-value steps in obtaining care. Today she'll be talking to us about sleep testing and post-covid-19 models of sleep care.

~~Sleep Testing~~ and Model~~s~~ of Care in the post-COVID-19 Era

Kathleen Sarmiento, MD MPH
Professor of Medicine, UC San Francisco
Executive Director, VHA National Sleep Medicine Program
San Francisco VA Health Care System
March 12, 2022



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The End.

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Conflict of Interest Disclosures for Speakers

☐ 1. I do not have any relationships with any entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, **OR**

■ 2. I have the following relationships with entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients.

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	ResMed
Consultant	
Speakers' Bureaus	
Financial support	
Other	

■ 3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

☐ 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

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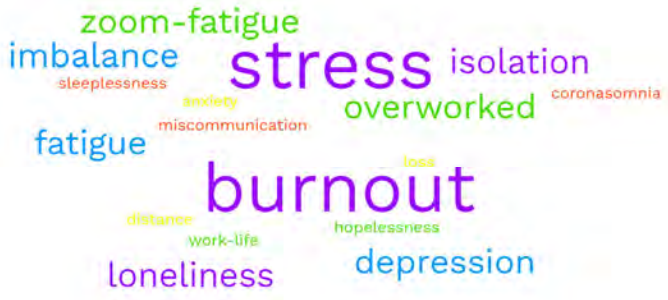
What's changed in the past two years?



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Positive Impacts of the Pandemic

- Culture and expectations about health care delivery have evolved
- Telehealth is the norm
- How we engage with patients and each other has been permanently altered
- More is possible than we previously thought
- Limitations and barriers lead to innovation

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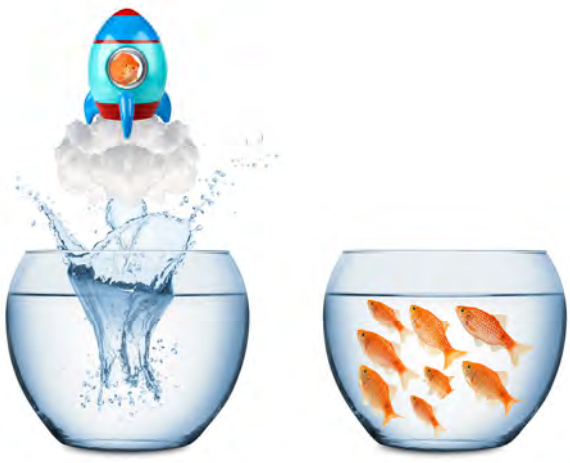
Cultivating an Environment of Innovation



VA **Everyone Else**

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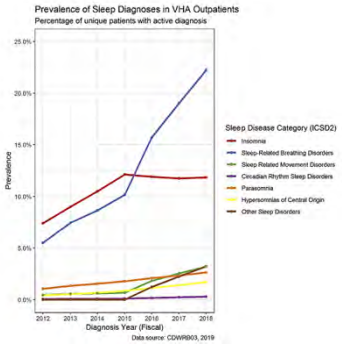
VA SLEEP MEDICINE: A DEMONSTRATION PROJECT

- Prevalence of sleep disorders increasing each year
- Rural Veterans are disproportionately impacted by limited access to sleep services
- New methods of care delivery were needed to increase access



Number and prevalence of sleep disorder diagnoses for Veterans who received care at VA medical facilities from FY2012-FY2018.

Categories	2012	2013	2014	2015	2016	2017	2018
	All Outpatients	All Outpatients	All Outpatients	All Outpatients	All Outpatients	All Outpatients	All Outpatients
	5,178,989	5,285,998	5,416,497	5,503,220	5,573,631	5,620,895	5,590,599
Insomnias	384,338 (7.42%)	475,018 (8.99%)	568,942 (10.5%)	667,472 (12.1%)	663,365 (11.9%)	660,604 (11.7%)	662,543 (11.8%)
Sleep-related breathing disorders	284,715 (5.5%)	393,241 (7.44%)	468,789 (8.65%)	559,773 (10.2%)	874,925 (15.7%)	1,070,070 (19%)	1,243,280 (22.2%)
Sleep-related movement disorders	23,747 (0.46%)	29,509 (0.56%)	33,174 (0.61%)	37,245 (0.68%)	101,560 (1.82%)	142,768 (2.54%)	178,183 (3.19%)
Circadian rhythm sleep disorders	2996 (0.06%)	4217 (0.08%)	4954 (0.09%)	5820 (0.11%)	9450 (0.17%)	12,934 (0.23%)	16,046 (0.29%)
Parasomnias	55,064 (1.06%)	70,920 (1.34%)	83,772 (1.55%)	98,639 (1.79%)	115,999 (2.08%)	131,655 (2.34%)	147,652 (2.64%)
Hypersomnias of central origin	21,737 (0.42%)	28,288 (0.54%)	36,915 (0.68%)	46,814 (0.85%)	63,040 (1.13%)	78,952 (1.4%)	95,387 (1.71%)
Other sleep disorders	601 (0.01%)	876 (0.02%)	1002 (0.02%)	1070 (0.02%)	68,676 (1.23%)	125,726 (2.24%)	180,847 (3.23%)

https://doi.org/10.1016/j.smrv.2020.101358

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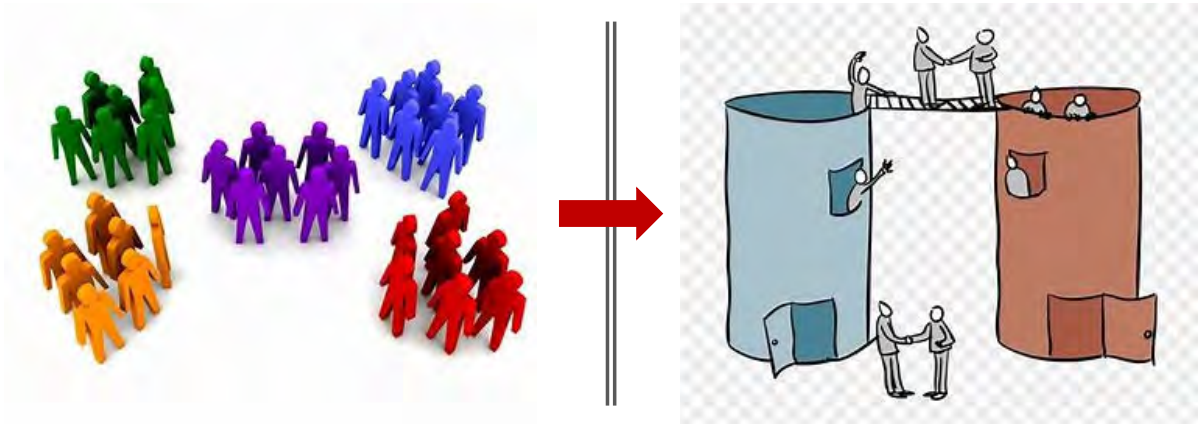

Innovation in Sleep Care Delivery

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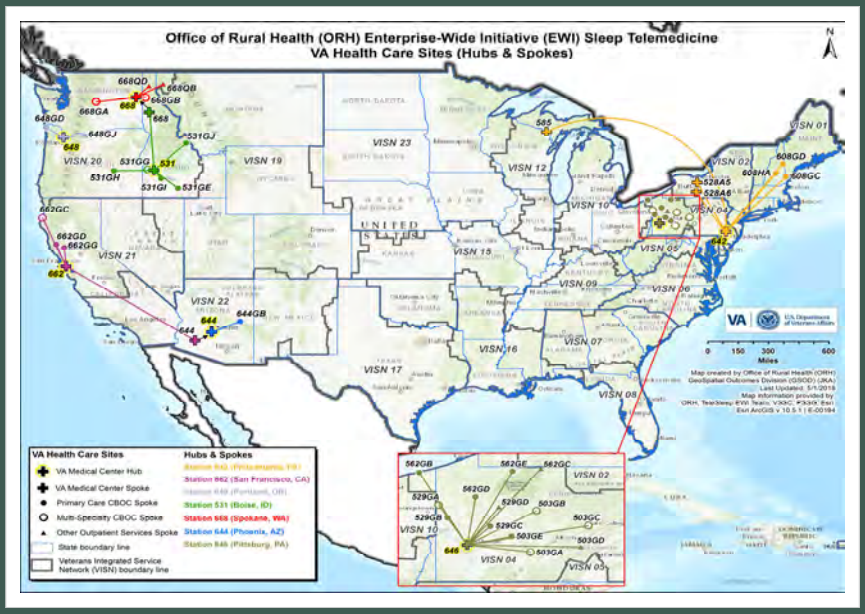

Office of Rural Health TeleSleep Program FY17

7 Hub Facilities
35 Spoke Facilities

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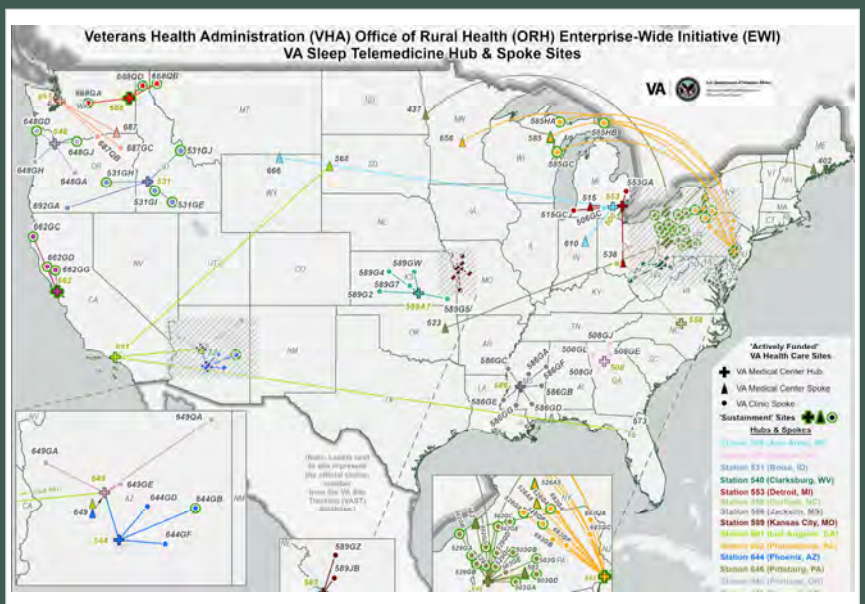

Office of Rural Health TeleSleep Program FY22

18 Hub Facilities
- 2 in sustainment
74 Spoke Facilities
- 10 in sustainment

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ORH TeleSleep Program

- Established in 2017 in response to an access crisis and need to deliver care differently
  - Hub-Spoke model
- Focused on reaching rural Veterans
- Emphasized using telehealth +/- deployment of travel teams
- Sought to create a roadmap for intra- and interfacility telehealth
- Aligned with VHA priorities and strategic plans
- Created a scalable and adaptable telehealth network
- Integrated evaluation in a learning health system model
  - Quantitative and qualitative assessments
  - Formative and summative evaluations

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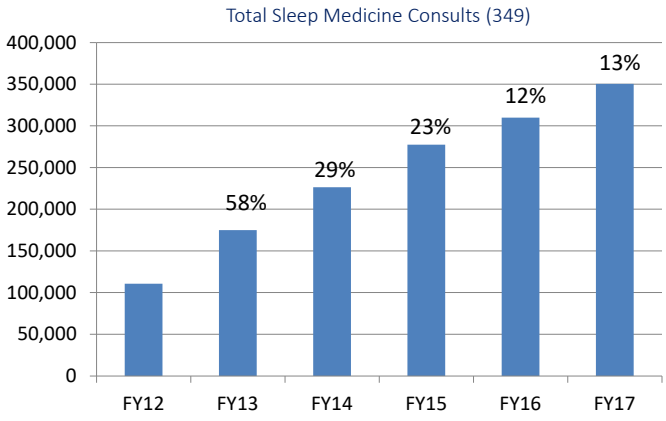
The Beginning

Limited Access to Sleep Care

- Long wait times for testing and clinics
- High cost, volume of outsourced care
- Lack of Standardization
- No central operations manual
- Siloed care within each VAMC
- Telehealth not common
- HSAT expansion active but with major barriers
- Remote monitoring of PAP possible but challenging between sites (lack of access)



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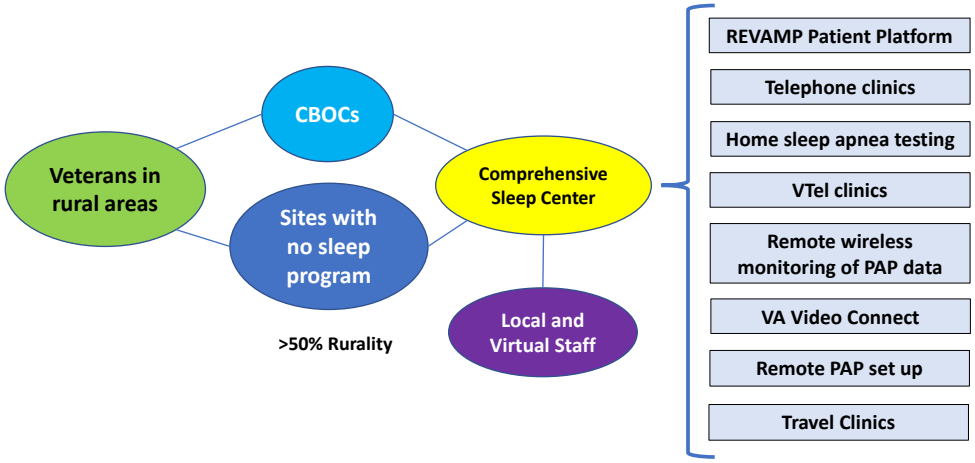
The Strategy: Create a high-performance TeleSleep network for Veterans in Rural Areas



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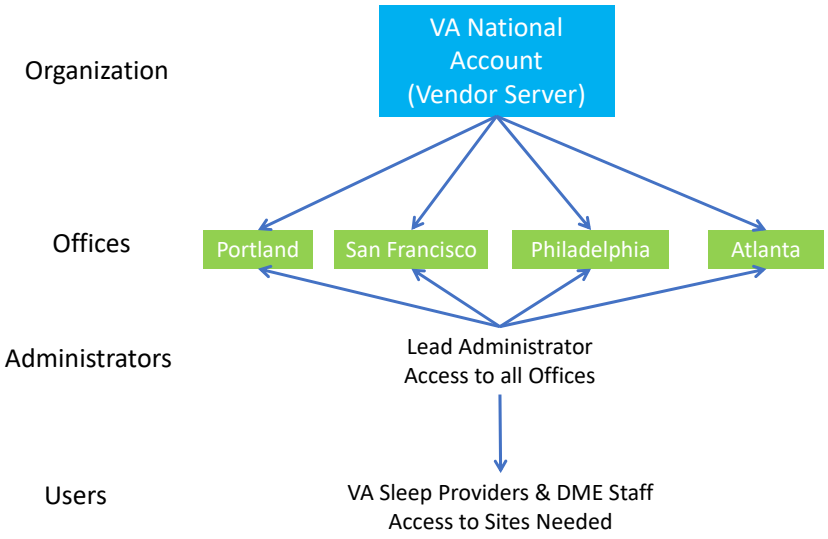
The Infrastructure: Remote Monitoring of PAP



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The Infrastructure: HSAT

- Multitude of brands in varying states of degradation/duct tape
- Data mapped to local area networks not easily accessed

- Several efforts were initiated to expand the use of HSAT
  - —Centralized resourcing of devices
  - —Standardizing national workflows and coding
  - —Implementation toolkits and support
  - —Provider and patient qualitative assessments

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HSAT ENABLES VETERANS TO CHOOSE VA

- HSAT is the most rapidly growing store-and-forward telehealth program in VA

- It allows hub-spoke partnerships to deliver care where a spoke site may otherwise outsource services to the community due to lack of an interpreting provider

- Testing capacity is limited by devices rather than “beds”

- Fills a gap where community sleep testing is also lacking

- Improves Veterans’ time to initiation of treatment by keeping care within VA

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Timeliness of care is impacted by method of sleep testing

- Long wait times and travel burden for in-lab studies influence the choice to use CITC
- Wait times are not necessarily shorter (and may be longer) in the community; delays in initiation of treatment are significant

TABLE 3. Number of Days From Referral to Treatment of Obstructive Sleep Apnea

	VA		Community Care		*P*	
Mean (SD)	Unmatched, N = 1347	Matched, N = 176	Fee Basis, N = 37	Choice, N = 51	VA (Matched) vs. Community Care	Fee Basis vs. Choice
Referral to sleep study (T0 to T1)	105.0 (77.3)	105.2 (62.2)	234.8 (147.7)	97.2 (76.3)	<0.001	<0.001
Sleep study to CPAP (T1 to T2)	29.2 (71.1)	24.4 (59.2)	73.4 (71.0)	113.9 (123.3)	<0.001	0.077
Referral to CPAP (T0 to T2)	134.2 (102.1)	129.6 (82.8)	308.2 (166.1)	211.1 (141.3)	<0.001	0.004

P-values are from *t* tests.
CPAP indicates continuous positive airway pressure; VA, Veterans Affairs.

SFVA Measurement Science QUERI

Kaul, et al Med Care 2020

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Barriers to Expansion of HSAT

Reasons Why VAMCs had no HSAT Programs

- Home sleep testing outsourced
- Insufficient technical staff
- Insufficient providers
- Insufficient funding
- Did not know it was available
- Not interested
- Never approved

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Centralized Resourcing of Devices

2,798 devices distributed nationally FY17-21

- Reduced overall wait times
- Improved Veteran satisfaction
- Increased study throughput
- Reduced Veteran travel burden
- Reduced Choice referrals
- Improved staff satisfaction
- Increased ability to partner with another VA
- Increased efficiency of sleep testing

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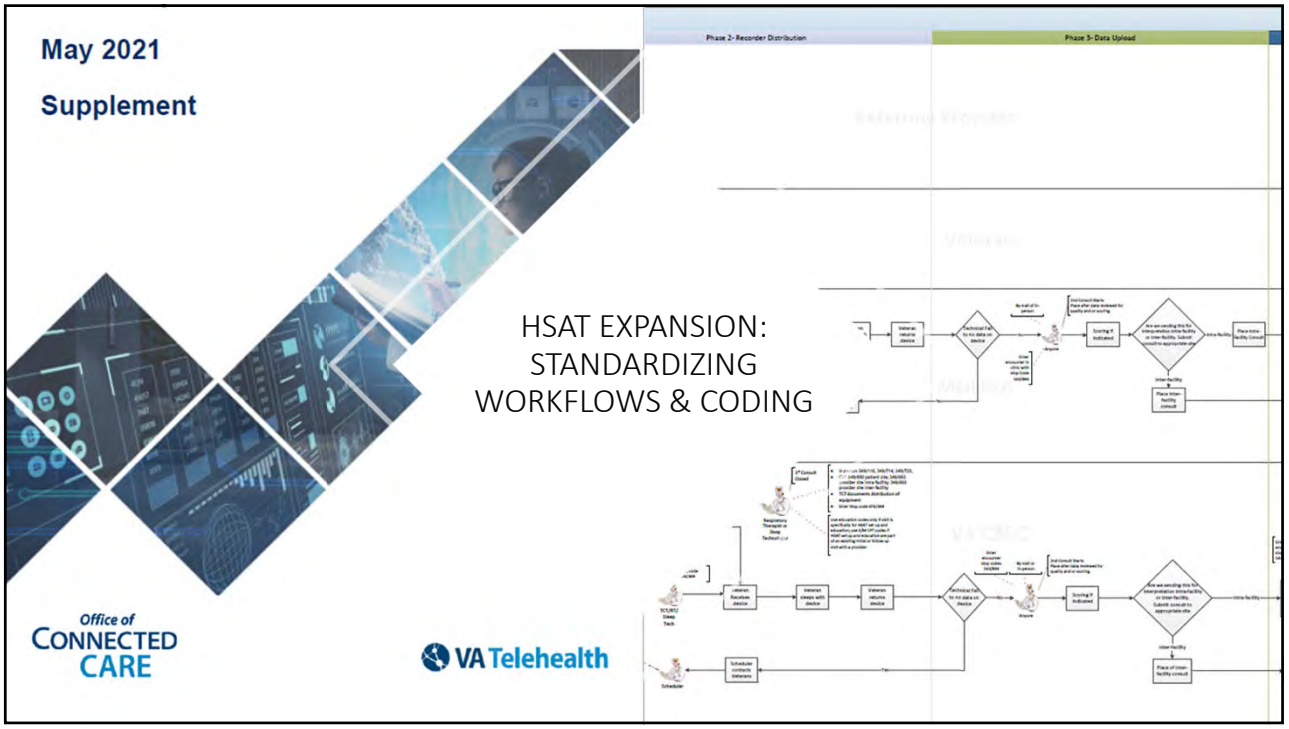

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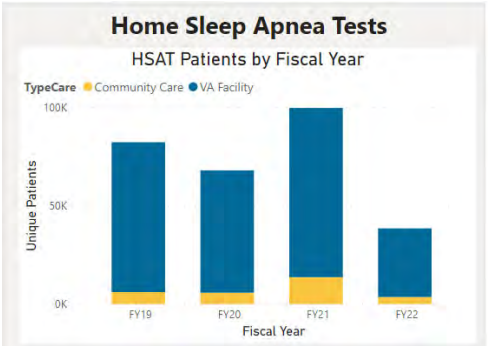
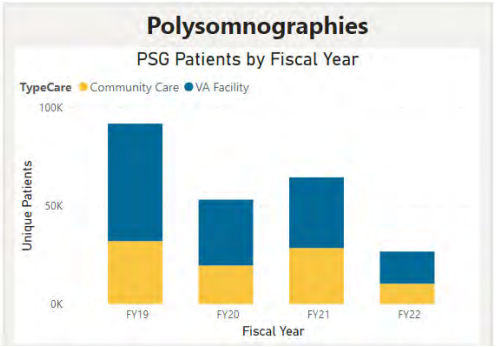
OUTCOMES OF HSAT EXPANSION

- 64 facilities (2013) → 132 facilities with HSAT (2022)
- 18 VA Medical Centers without HSAT programs *or* without providers to interpret sleep studies (partnered via IFC)





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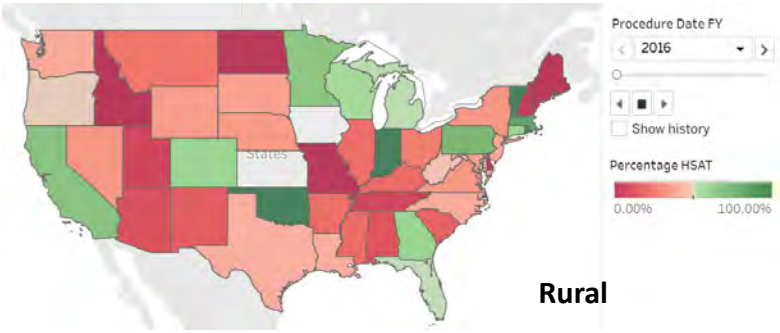
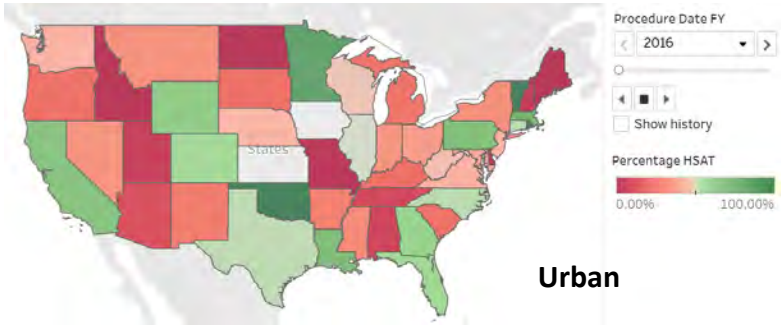
HSAT use: 2016



Rural



Urban

Unpublished; CDWRB03

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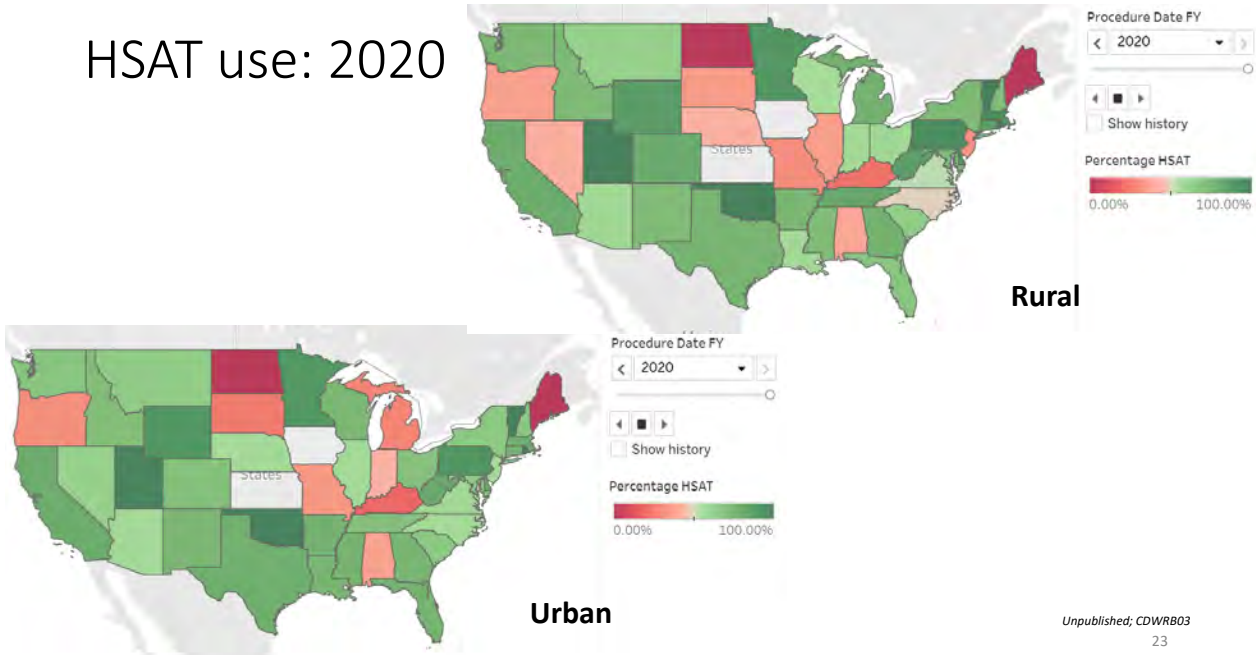
HSAT use: 2020



Unpublished; CDWRB03

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OUTCOMES OF HSAT EXPANSION

HSAT enabled sleep programs to recover from testing backlogs secondary to the PHE

- Overall decrease in total sleep testing volume largely attributable to decline in PSGs
- Significant increase in HSAT use in FY21 after labs reopened

FY	Uniques	Encounters	HSAT	PSG
19	490,886	885,017	75,728	59,278
20	522,270	993,435	81,597	36,904
21	565,876	1,157,637	113,374	40,687

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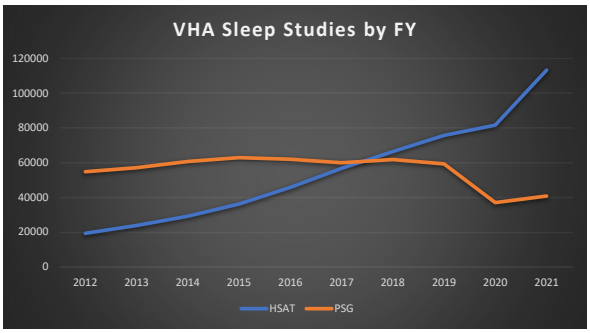
- Expansion of HSAT programs has reduced CITC

National Summary	FY19	FY20	FY21
Paid Claims	$45,294,705	$44,337,193	$38,061,677

Pyramid Analytics (va.gov)

- HSAT reaches Veterans living further from VA facilities, reducing travel burden



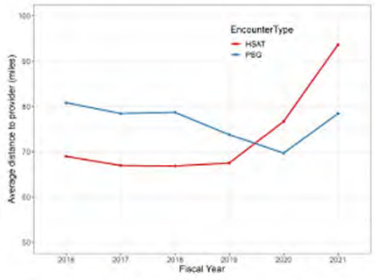


Figure 3. Average Euclidean distance ("as the crow flies") from patient's home to nearest VA facility among patients who completed HSAT (red line) and PSG (blue line) sleep testing during FY16-21.

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Qualitative Interviews: HSAT

- Positive experience with few equipment or connectivity issues
- Veterans completing both PSG and HSAT preferred HSAT due to difficulty sleeping in a laboratory
- HSAT eliminated the dual challenge of traveling to and falling asleep in a lab setting
- Testing through community associated with lack of notification of results and frustration with being unable to obtain recommended PAP therapy

SFVA Measurement Science QUERI
Nicosia et al, BMC Health Serv Res 2021

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Experience with sleep-apnea testing

- Have you participated in testing for sleep apnea/sleep problems? If yes: Did you do this testing at home or did you stay overnight for testing in a sleep lab?
- If at home: Tell me about your experience using the testing equipment at home. What worked well about home testing? What didn't work?
  - How well does it work to connect the testing equipment where you live? Is there adequate cell coverage in your area to transmit data from the testing equipment?
- If at lab: Tell me about your experience going to the lab for testing. What did you like? What didn't you like?

"It [in-lab testing] was more like an awake study, it was hard to fall asleep."

"simple" and "self-explanatory."

"I live where it's very, very rural. There's a lot of lakes and hills and valleys. So for me to get to the local clinic, it's a good 40 to 45-minute drive from where I live. So it's not an easy day when I have to go there and back."

"I gotta drive three and a half hours up there, in the day. And then I'm supposed to calm down and sleep with all of these wires on me, and then as soon as they're done at like 7 o'clock in the morning you're just, you're sent home. And so now I'm exhausted and I gotta drive three and a half hours home."

Nicosia et al, BMC Health Serv Res 2021
SFVA Measurement Science QUERI

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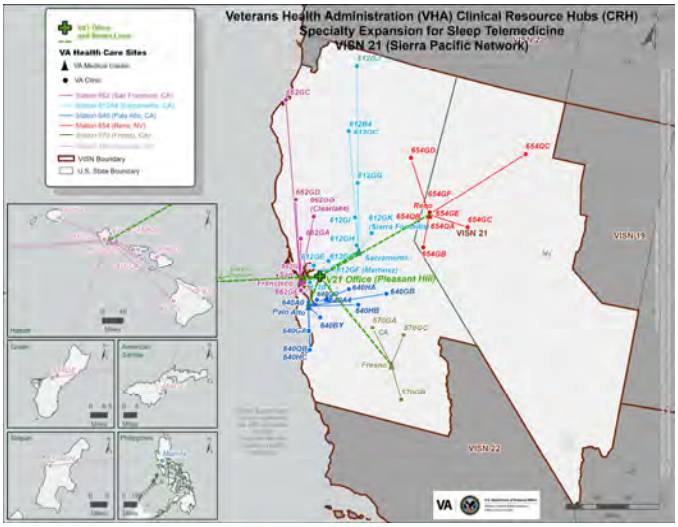
VA's Clinical Resource Hubs

Regional Networks of shared resources

- Built as a shared resource
  - FTEE located across sites
  - Virtual Teams
- Augments gaps in care
- Cultivates community across sites
- Enables Veterans to Choose VA



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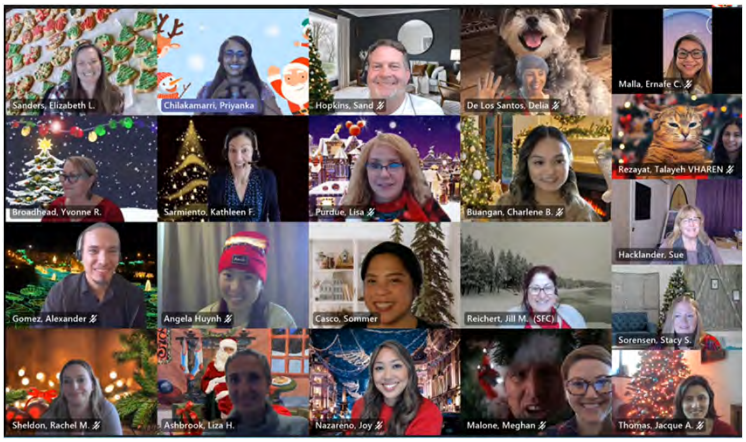
Sleep CRH: Where are we?



- San Francisco, CA
- Honolulu, HI
- San Diego, CA
- Reno, NV
- Oakland, CA
- Sacramento, CA
- New York, NY
- Fayetteville, AR
- Tampa, FL
- Fresno, CA
- Seattle, WA
- Birmingham, AL

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Sleep Clinical Resource Hubs

<u>Strategic Direction</u>

Purpose

- Providers can easily connect Veterans with the sleep care they need, wherever they are – in a convenient way that is financially sustainable for VA

Mission

- Expand Veteran access to sleep care and reduce disparities

Approach

- Augment Sleep care at facilities needing greater capacity

Tagline

- Better Sleep, Better Health!

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- Reduce sleep-related community care volume and cost by augmenting access to VA Sleep care when access standards can't be met at a local facility
- Create a "One VA" experience for Veterans, bringing care to them locally, regardless of where CRH staff are located
- Standardize processes and workflows through the network
- Stabilize the workforce in VISN 21 in sleep medicine by creating community and a collaborative network, reducing turnover
- Provide an environment with high-risk tolerance to explore new models of shared resources
- Provide a roadmap that other specialties and hubs may adopt as specialty care programs expand

V21 Sleep CRH Goals

Better Sleep, Better Health!

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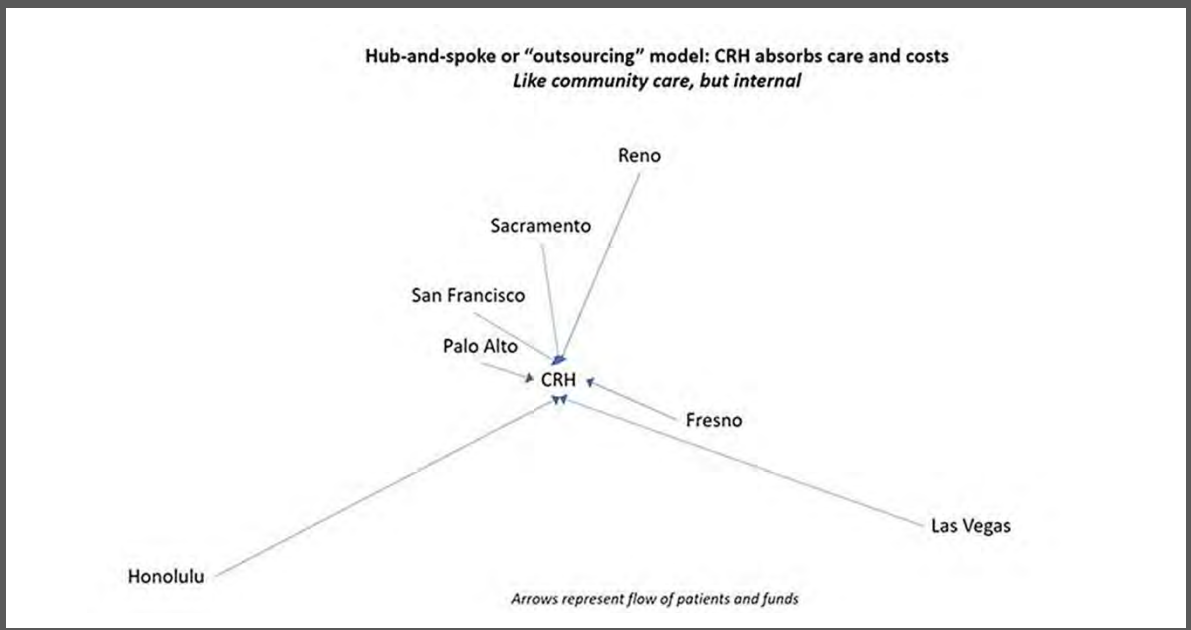

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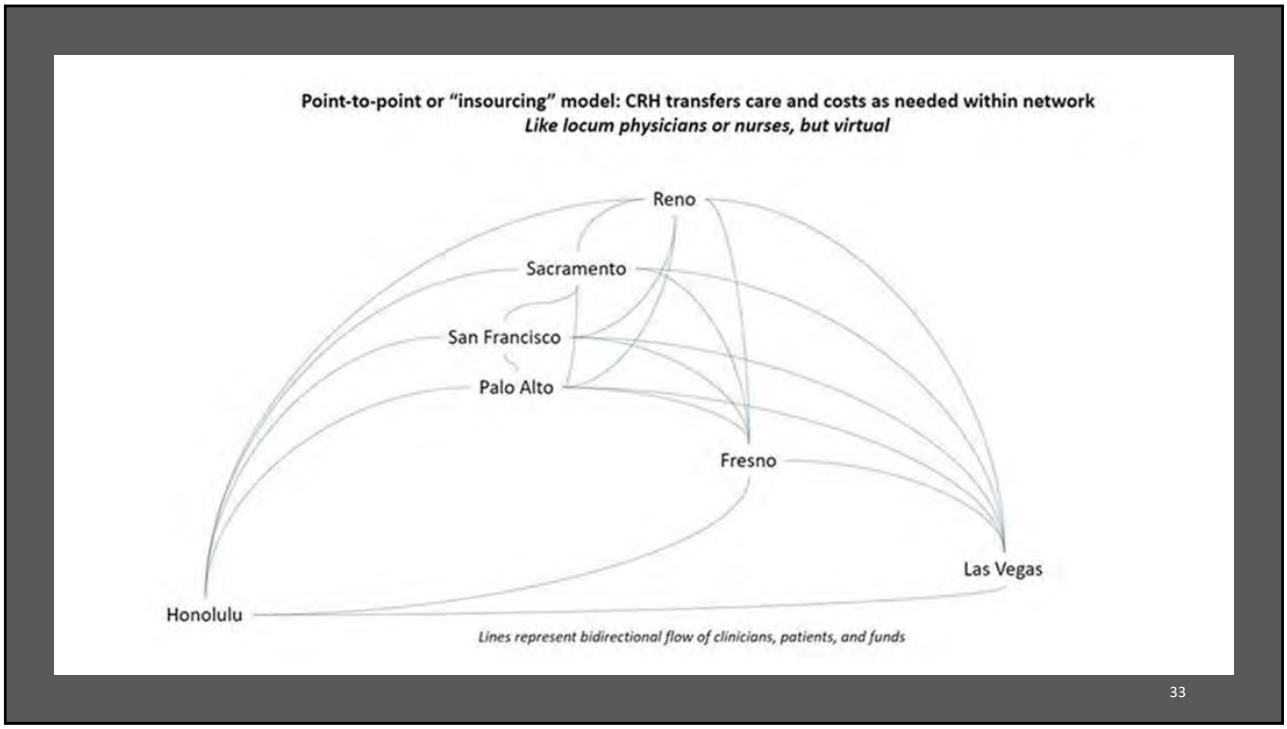

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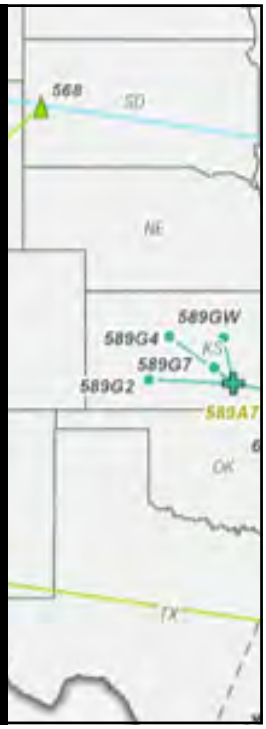
Sleep CRH: Where do we provide services?

- San Francisco
- Sacramento
- Fresno
- Reno
- Las Vegas
- Honolulu
- Guam
- American Samoa
- Grand Junction, CO
- Sheridan, WY



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Lessons Learned from both programs

- Home sleep testing doesn't work well by mail for reusable recorders
- Embedding them within Veterans' communities increases timely returns and reduces lost recorders
- HSAT innovation is needed for use in hypoventilation syndromes
- Integrating with a Veteran's home facility as if you're a local provider provides the best care coordination for the Veteran and for the local team
- New models of care are like start-ups. They take time, are an upfront investment with long-term gains

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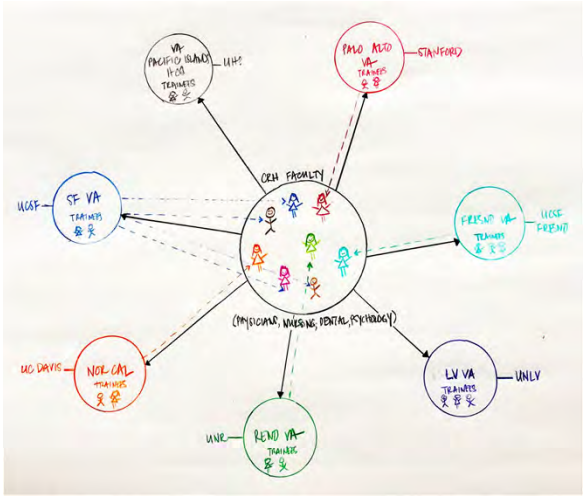
Education Too?

- Engagement of trainees & hub faculty across sites
  - V21 Innovation in educational model: Sleep pilot
  - Enhances education from niche specialists
  - Stabilizes training programs
  - Medical, Dental, Psychology trainees



CRH Education Model: CRH faculty are represented in the center black circle. Individual healthcare systems are represented as satellite spokes, along with possible academic affiliates (for physician, dental, psychology, or nursing schools). Dotted lines from a healthcare system to the CRH represent a faculty member affiliated with that healthcare system's academic institution

36

Challenges + Barriers = Innovation

37

What would innovation in health care delivery look like for YOU?

38

Telehealth in the Era of the COVID-19 Pandemic

Current changes

- Temporary removal of policies limiting the use of telehealth
- Medicare reimbursement
- Temporary waiving of licensure requirements by states
- Payment parity policies implemented
- Rising number of Medicaid patients

39

3 Types of Telehealth for Medicare Beneficiaries

Summary of Medicare Telemedicine Services

TYPE OF SERVICE	WHAT IS THE SERVICE?	HCPCS/CPT CODE	Patient Relationship with Provider
MEDICARE TELEHEALTH VISITS	A visit with a provider that uses telecommunication systems between a provider and a patient	Common telehealth services include: • 99201-99215 (Office or other outpatient visits) • G0425-G0427 (Telehealth consultations, emergency department or initial inpatient) • G0406-G0408 (Follow-up inpatient telehealth consultations furnished to beneficiaries in hospitals or SNFs) For a complete list: https://www.cms.gov/Medicare/Medicare-General-Information/Telehealth/Telehealth-Codes	For new* or established patients. *To the extent the 1135 waiver requires an established relationship, HHS will not conduct audits to ensure that such a prior relationship existed for claims submitted during this public health emergency
VIRTUAL CHECK-IN	A brief (5-10 minutes) check in with your practitioner via telephone or other telecommunications device to decide whether an office visit or other service is needed. A remote evaluation of recorded video and/or images submitted by an established patient.	• HCPCS code G2012 • HCPCS code G2010	For established patients.
E-VISITS	A communication between a patient and their provider through an online patient portal.	• 99421 • 99422 • 99423 • G2061 • G2062 • G2063	For established patients.

MEDICARE TELEMEDICINE HEALTH CARE PROVIDER FACT SHEET | CMS

40

Medicare Telehealth Visits

- *Effective for services starting March 6, 2020 and for the duration of the COVID-19 Public Health Emergency, Medicare will make payment for Medicare telehealth services furnished to patients in broader circumstances.*
- *These visits are considered the same as in-person visits and are paid at the same rate as regular, in-person visits.*
- *Starting March 6, 2020 and for the duration of the COVID-19 Public Health Emergency, Medicare will make payment for professional services furnished to beneficiaries in all areas of the country in all settings.*
- *While they must generally travel to or be located in certain types of originating sites such as a physician's office, skilled nursing facility or hospital for the visit, effective for services starting March 6, 2020 and for the duration of the COVID-19 Public Health Emergency, Medicare will make payment for Medicare telehealth services furnished to beneficiaries in any healthcare facility and in their home.*
- *The Medicare coinsurance and deductible would generally apply to these services. However, the HHS Office of Inspector General (OIG) is providing flexibility for healthcare providers to reduce or waive cost-sharing for telehealth visits paid by federal healthcare programs.*
- *To the extent the 1135 waiver requires an established relationship, HHS will not conduct audits to ensure that such a prior relationship existed for claims submitted during this public health emergency.*

MEDICARE TELEMEDICINE HEALTH CARE PROVIDER FACT SHEET | CMS

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Virtual Check-Ins

Virtual Check-Ins enable patients to communicate with providers to avoid unnecessary trips to the doctor's office

- *Virtual check-in services can only be reported when the billing practice has an established relationship with the patient.*
- *This is not limited to only rural settings or certain locations.*
- *Individual services need to be agreed to by the patient; however, practitioners may educate beneficiaries on the availability of the service prior to patient agreement.*
- *HCPCS code G2012: Brief communication technology-based service, e.g. virtual check-in, by a physician or other qualified health care professional who can report evaluation and management services, provided to an established patient, not originating from a related e/m service provided within the previous 7 days nor leading to an e/m service or procedure within the next 24 hours or soonest available appointment; 5-10 minutes of medical discussion.*
- *HCPCS code G2010: Remote evaluation of recorded video and/or images submitted by an established patient (e.g., store and forward), including interpretation with follow-up with the patient within 24 business hours, not originating from a related e/m service provided within the previous 7 days nor leading to an e/m service or procedure within the next 24 hours or soonest available appointment.*
- *Virtual check-ins can be conducted with a broader range of communication methods, unlike Medicare telehealth visits, which require audio and visual capabilities for real-time communication.*

MEDICARE TELEMEDICINE HEALTH CARE PROVIDER FACT SHEET | CMS

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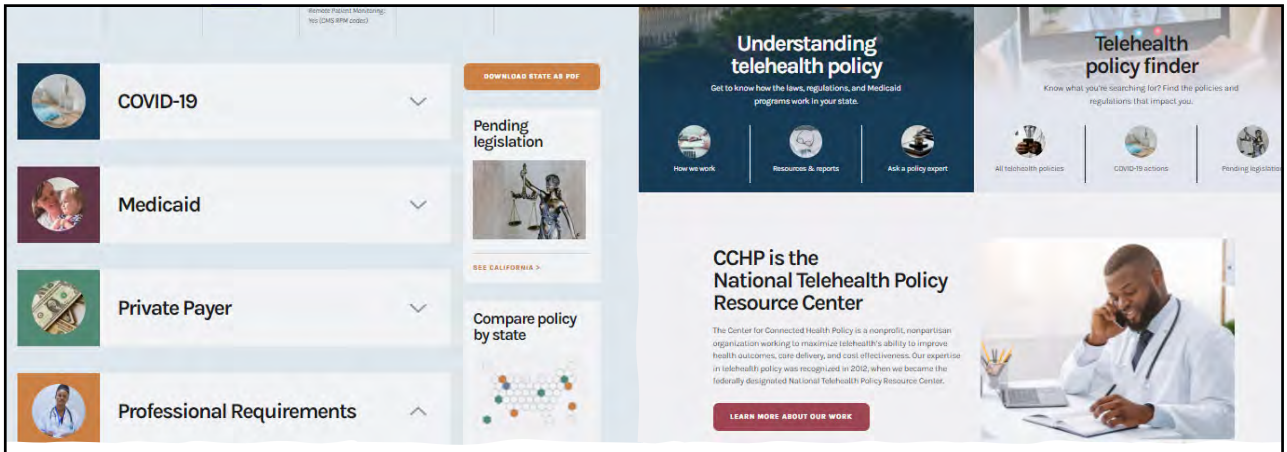
E-Visits

- *These services can only be reported when the billing practice has an established relationship with the patient.*
- *This is not limited to only rural settings. There are no geographic or location restrictions for these visits.*
- *Patients communicate with their doctors without going to the doctor's office by using online patient portals.*
- *Individual services need to be initiated by the patient; however, practitioners may educate beneficiaries on the availability of the service prior to patient initiation.*
- *The services may be billed using CPT codes 99421-99423 and HCPCS codes G2061-G206, as applicable.*
- *The Medicare coinsurance and deductible would generally apply to these services.*

MEDICARE TELEMEDICINE HEALTH CARE PROVIDER FACT SHEET | CMS

43

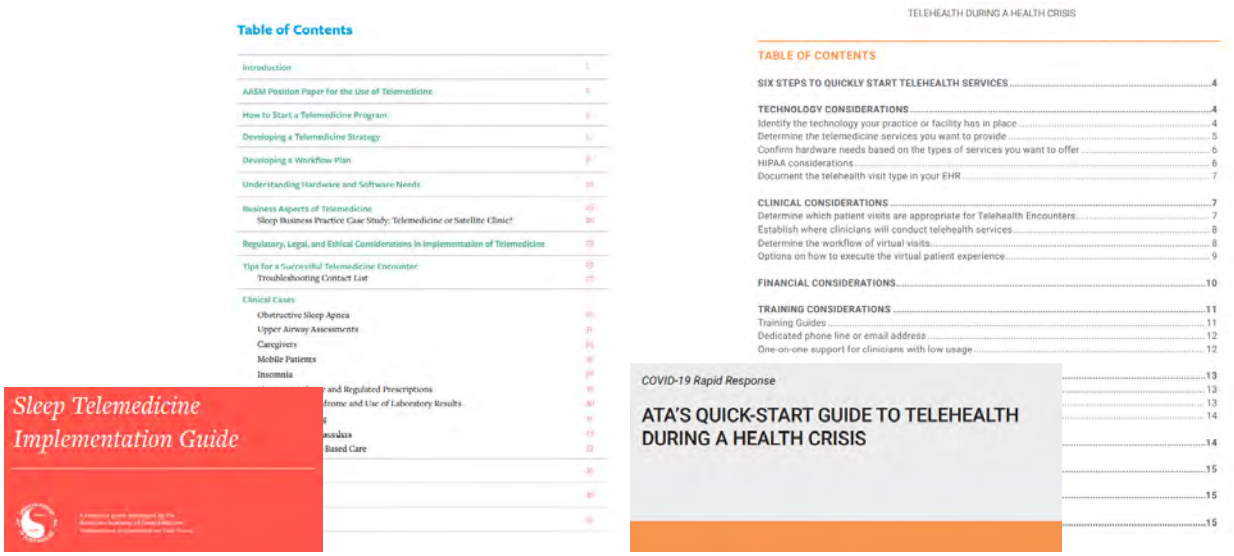


National Telehealth Policy Resource Center

Home | Center for Connected Health Policy (cchpca.org)

44

TM Implementation Resources



45

Resources

- Policy - ATA (americantelemed.org)
- Home | Center for Connected Health Policy (cchpca.org)
- Coverage and Payment Related to COVID-19 Medicaid and CHIP (cms.gov)
- MEDICARE TELEMEDICINE HEALTH CARE PROVIDER FACT SHEET | CMS
- 2018-24170.pdf (govinfo.gov)

46

Summary

- Things have changed significantly post-COVID-19
- Temporary waivers for telehealth remain in effect during the PHE
- Decisions to convert temporary to permanent waivers supporting telemedicine post-PHE are made state-by-state
- Innovation in how and where we work is possible!

Come to the dark side . . . join VA!

47

Alternatives to Positive Airway Pressure Therapy for Sleep Disordered Breathing

9:05 a.m. – 9:50 a.m.

ROBSON CAPASSO, MD
STANFORD UNIVERSITY

Dr. Robson Capasso is the Chief of Sleep Surgery, Professor of Otolaryngology and Head and Neck Surgery and Associate Dean at Stanford University School of Medicine and Advisor to the Stanford Byers Center for Biodesign. His medical training includes Head and Neck Surgery, Neurosciences and Sleep Medicine. He has done research and published extensively on the pre-treatment evaluation and surgical treatment of obstructive sleep apnea and currently his research interests have a focus on the analysis of clinically relevant outcomes and value-based strategies for sleep health. The local and international recognition of this work is often associated with one of his favorite tasks: lecturing and trading knowledge nationally and internationally. He has mentored or supervised hundreds of medical students, residents, fellows or visiting scholars from over 30 countries, and dozens of Stanford Biodesign students who developed healthcare projects orcompanies in the Bay Area, Japan, Brazil and Singapore. He aims to utilize this acquired experience to foster health innovation training of multidisciplinary teams and engineers with broad impact globally. He is a member of the Stanford Medical Leadership Academy, an initiative aiming to foster the development of innovative leadership across and outside departments at the School of Medicine and in the role of Associate Dean of Virtual Medicinehe assists the Dean's office and our CTSA group for the strategic development of translational research and education.

Most importantly, Robson is Cintia's husband, Julia, Lucas and Olivia's father, world traveler, Palmeiras' fan and tennis enthusiast.

Sleep Surgery (and some things non-CPAP): Essentials

Robson Capasso M.D.
Professor, Chief of Sleep Surgery
Associate Dean
Stanford University school of medicine

Stanford MEDICINE | Otolaryngology Head & Neck Surgery

1

Disclosures

- SAB
  - Invicta Medical
  - Bryte LLC
  - Focused on surgery…

2

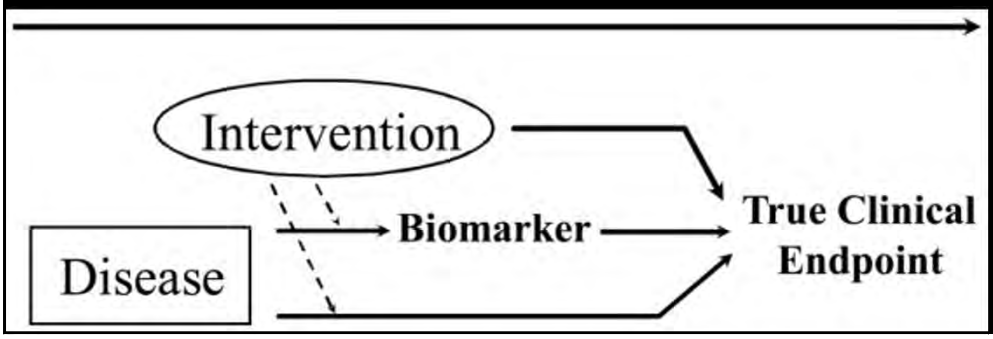
April 27, 2018

Be Skeptical About Biomarkers and Surrogate Endpoints

By Mike Lauer, M.D.
NIH Deputy Director for Extramural Research

Many of us remember where we were when a sentinel event occurred—when President Kennedy was assassinated or planes crashed into the World Trade Center towers. For cardiologists, we remember where we were when we heard the preliminary results of the "Cardiac Arrhythmia Suppression Trial" (otherwise known as CAST) on August 10, 1989.

Let me explain. In the 1980s, a large body of research showed that patients who survived a heart attack (the technical term is myocardial infarction) and who had lots of skipped beats—heart beats that occurred out of synch with the regular heart beat (the technical term is ventricular premature beat or VPB)—had an unusually high risk of sudden death from an electrical storm that effectively disables the heart within a matter of minutes. In other words, among heart attack survivors, the presence of VPBs was a "biomarker" or "surrogate endpoint" of increased risk of sudden death.



3

Reviewing the Systematic Reviews in OSA Surgery

Victor Certal, MD[1,2], Naoya Nishino, MD[3], Macario Camacho, MD[4], and Robson Capasso, MD[4]

Otolaryngology—Head and Neck Surgery
XX(X) 1–13

DOI: 10.1177/0194599813509959
http://otojournal.org
SAGE

- 18-90%
  - Type, number of surgeries.
    - Significant variability even for the same surgery
  - Outcome - AHI.

Cereal V, Nishino N, Camacho M, Capasso R. Reviewing the Systematic Reviews in OSA Surgery Otolaryngol Head Neck Surg. 2013 Dec;149(6):817-29

4

No, mild or severe ?

```
RESPIRATORY ANALYSIS:  (index = #/hr)
Apnea/Hypopnea Index (AHI): 23.0
*AHI 4% or greater: 0.3

Respiratory Disturbance Index (RDI): 42.3

Apneas (index, #): 0.0  (0)
Obstructive Apneas (index, #): 0.0  (0)
Mixed Apneas (index, #): 0.0  (0)
Central Apneas (index, #): 0.0  (0)
Hypopneas (index, #): 23.0  (162)
RERAs (index, #): 19.3  (136)

Mean Awake SpO2: 97%
Mean Sleep SpO2: 97%
Minimum Sleep SpO2: 93%
Sleep Time with SpO2 < 88% (min, % of TST): 0.0  (0.0%)
```

5

"Must" Treat x "Nice" to treat?

Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study

P Heinzer, S Vat, P Marques-Vidal, H Marti-Soler, D Andries, N Tobback, V Mooser, M Preisig, A Malhotra, G Waeber, P Vollenweider, M Tafti,* J Haba-Rubio*

Findings The median apnoea-hypopnoea index was 6·9 events per h (IQR 2·7–14·1) in women and 14·9 per h (7·2–27·1) in men. The prevalence of moderate-to-severe sleep-disordered breathing (≥15 events per h) was 23·4% (95% CI 20·9–26·0) in women and 49·7% (46·6–52·8) in men. After multivariable adjustment, the upper quartile

6

SPECIAL ARTICLES

JCSM
Journal of Clinical Sleep Medicine
http://dx.doi.org/10.5664/jcsm.2172

Rules for Scoring Respiratory Events in Sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events

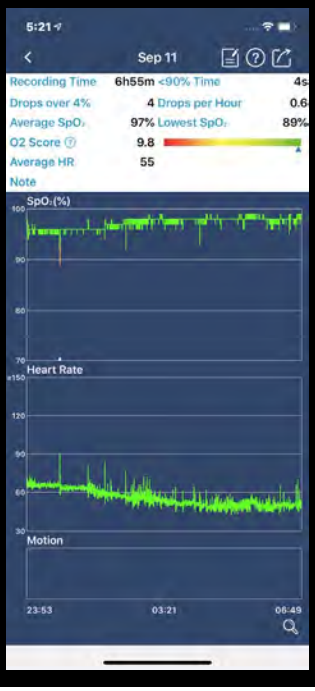
Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine

Hypopnea Summary

The above discussion outlines the difficulties in choosing a single definition for hypopnea. Although there were dissenters, the task force reached consensus on a definition of a hypopnea rule in adults using a 30% drop in the nasal pressure excursion for 10 seconds or greater associated with ≥ 3% desaturation OR an arousal. The majority of the task force felt that a hypopnea definition based only on desaturation would result in misdiagnosis of some patients in whom respiratory events fragment sleep but result in minor drops in the SpO_2. While there seems little doubt that cardiovascular morbidity is associated with oxygen desaturation, the goals of OSA treatment address a much wider range of symptoms including daytime sleepiness,

7

Wellue
FDA Cleared



8

8

SKUP3 - UPPP RCT (Friedman I-II, BMI<36)

	SSS Suh	SSS Srvw	Frqwur# Suh	Frqwur# srvw
DKL	8616	5414	8519	791;
DL	731;	4519	7518	67
UGL	8819	581;	871:	8314
ODI	**44.6**	**14**	7414	6819

Browaldh N, et al. Thorax 2013;68:846–853

9

CLINICALLY RELEVANT OUTCOMES

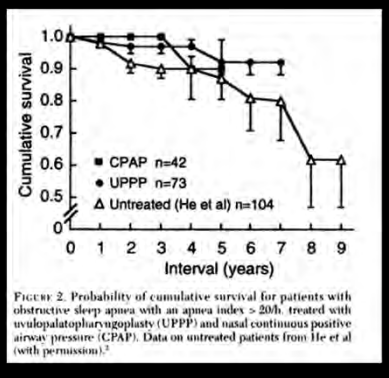
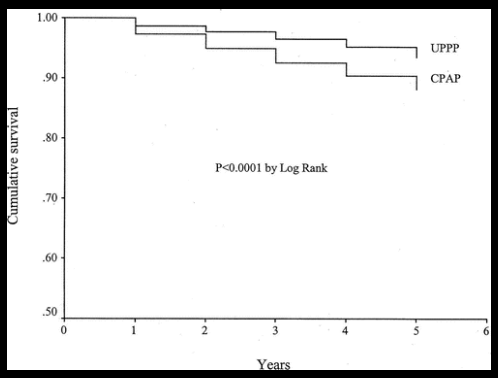


FIGURE 2. Probability of cumulative survival for patients with obstructive sleep apnea with an apnea index > 20/h, treated with uvulopalatopharyngoplasty (UPPP) and nasal continuous positive airway pressure (CPAP). Data on untreated patients from He et al (with permission).[3]



OHNS 2004 Jun;130(6):659-65

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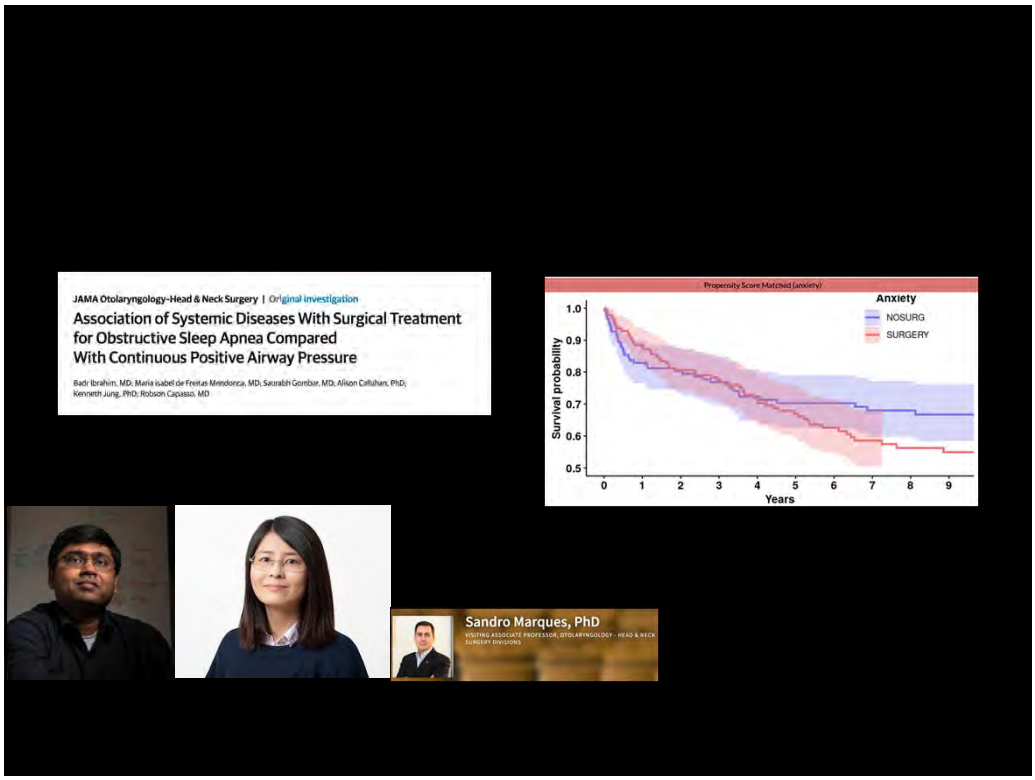

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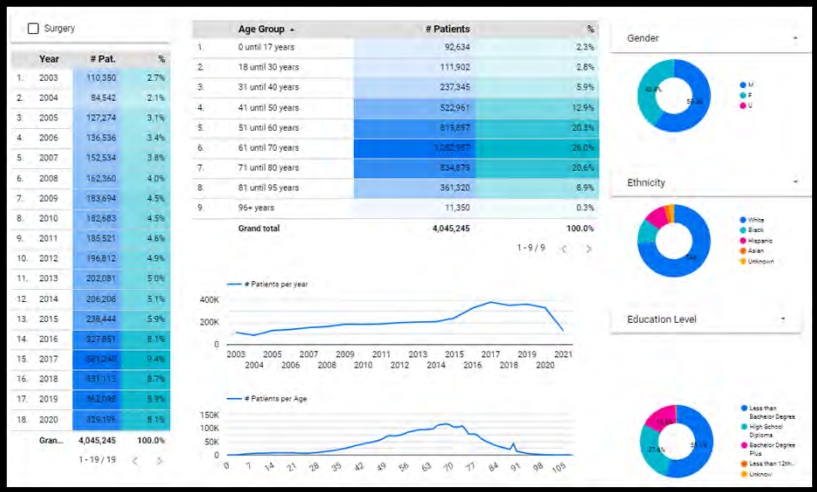


RWE4S: we aim to explore large datasets/wearables, understand the characteristics and unmet needs on sleep health.

12

1st: Why?

- Need better biomarkers (digital, molecular, etc...) AHI is not it.
- Snoring X Daytime sx's X CV, neurological/behavioral and other clinically relevant outcomes.

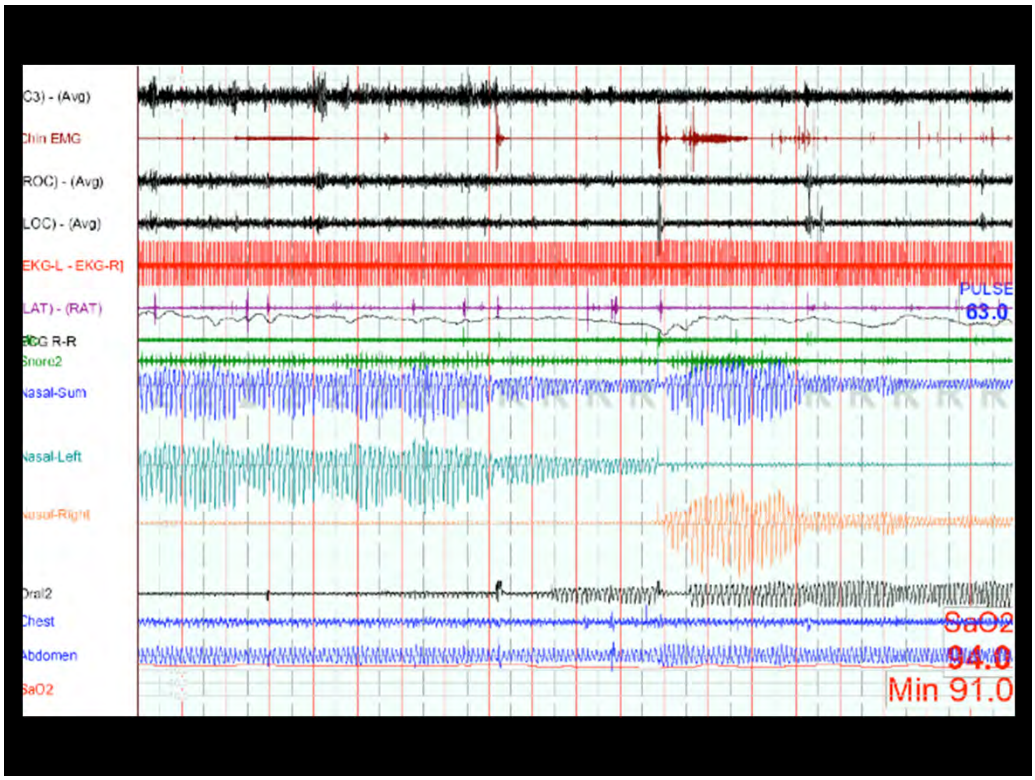
13

THE BIG 7

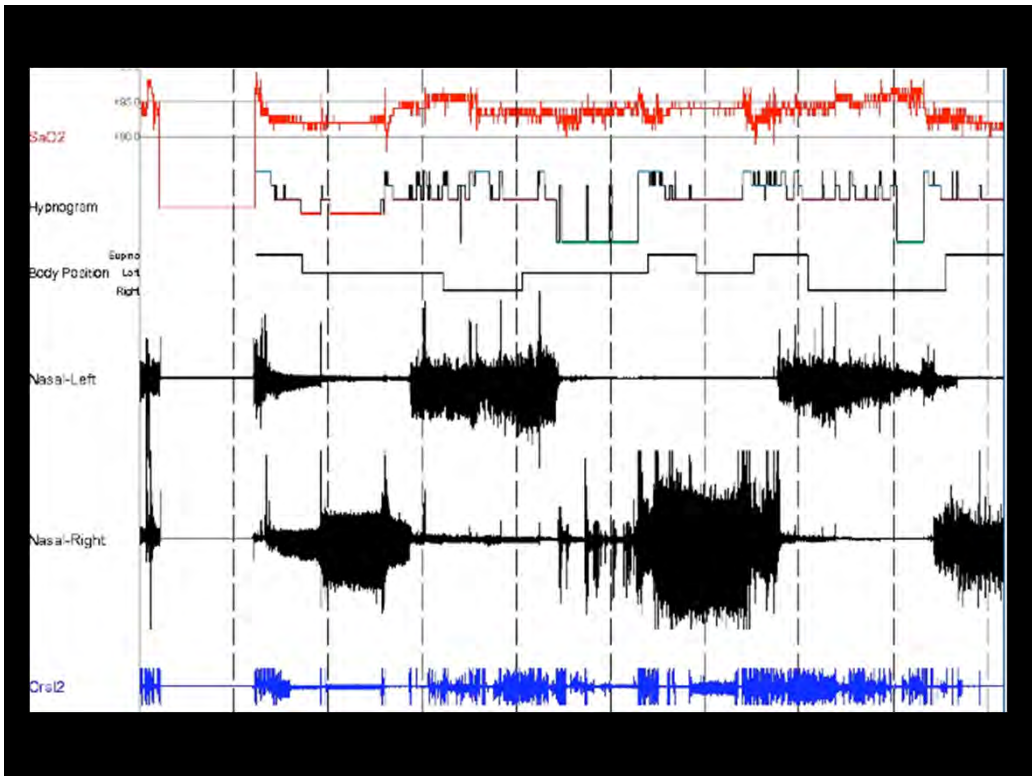
Relationship

- Nasal cavity
- Oropharyngeal anatomy
- Cervico-facial skeleton, Occlusion
- BMI
- Age
- Positional component
- Meds: muscle relaxants, benzodiazepines, opioids

14


C3) - (Avg)
Chin EMG
ROC) - (Avg)
LOC) - (Avg)
EKG-L - EKG-R]
LAT) - (RAT)
ECG R-R
Snore2
Nasal-Sum
Nasal-Left
Nasal-Right
Oral2
Chest
Abdomen
SaO2
PULSE
63.0
SaO2
94.0
Min 91.0

15


SaO2
Hypnogram
Body Position
Supine
Left
Right
Nasal-Left
Nasal-Right
Oral2

16

Nose and Sleep:

- Route of breathing changes dynamically during sleep
- Oro-nasal transitions may cause arousals/ sleep instability.
- It may happens without significant AHI changes or desaturations

Hsia J, Camacho M, **Capasso R.** *Sleep and Breathing* 2014 Mar;18(1):159-64.

Sullivan S, Carrillo O, **Capasso R.** Rhinologic Aspects of Sleep Disordered Breathing.. *Rhinology, Diseases of the Nose, Sinuses and Skull Base. First Edition.* Editors Peter Hwang and David Kennedy, Thieme Publications, May 2012.

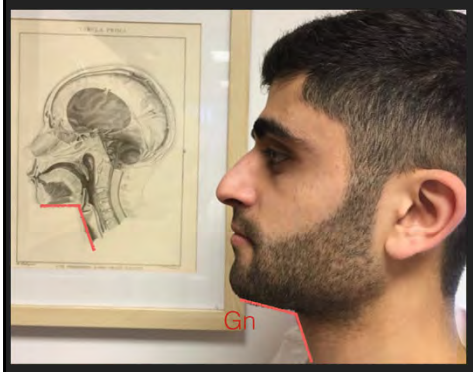
17

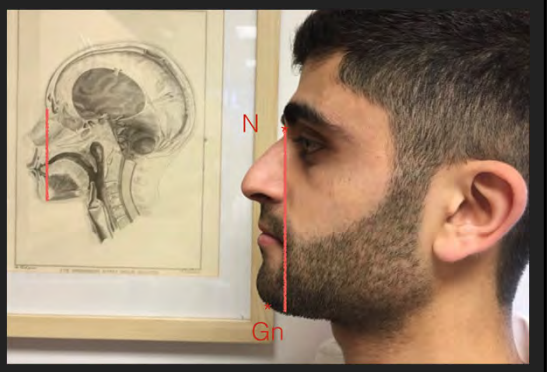
Oral cavity

18

THE BIG 7

Cervico-mental angle / Gonzales-ulloa





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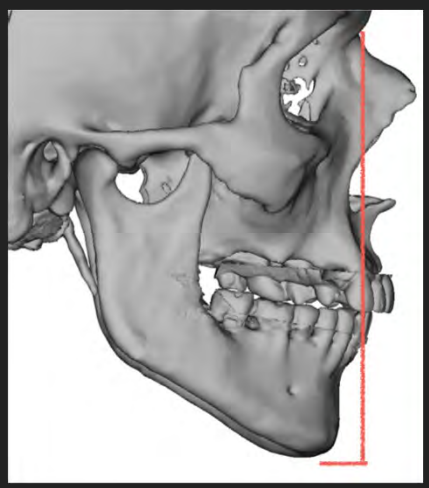
THE BIG 7

skeletal deficiencies



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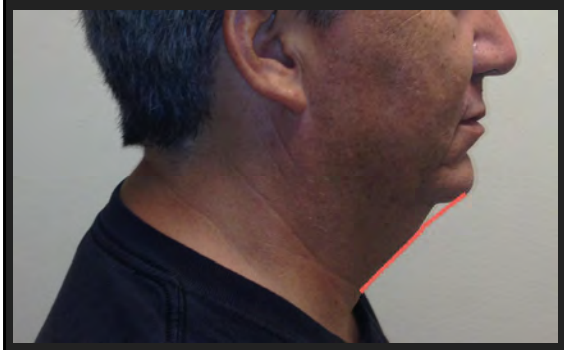


Obtuse angle:

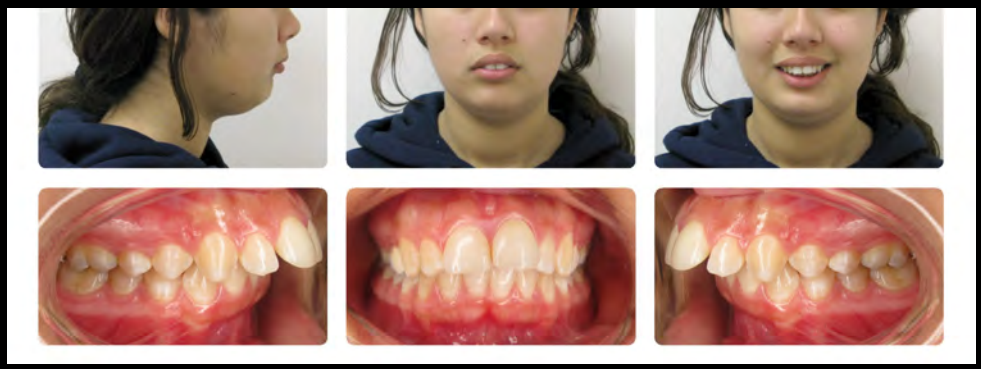
Neck adiposity

Anterior-inferior hyoid, increased pharyngeal length. Yu et al Chest 2003

Poorly developed mandible.

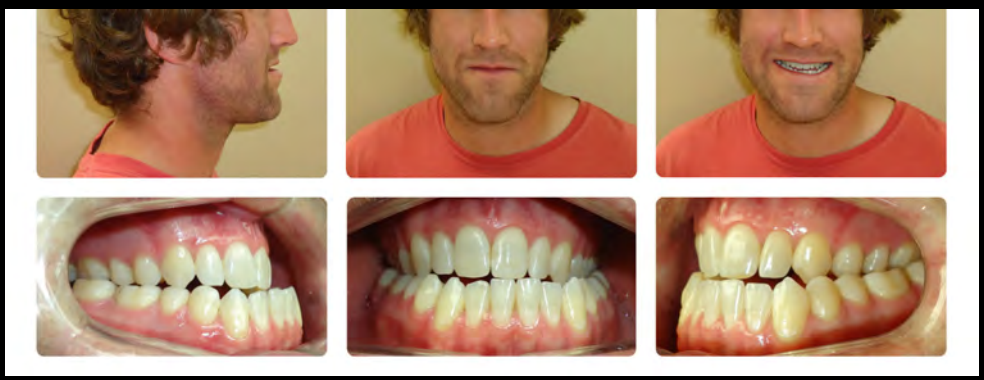
21

Mandibular deficiency



22

Maxillary deficiency



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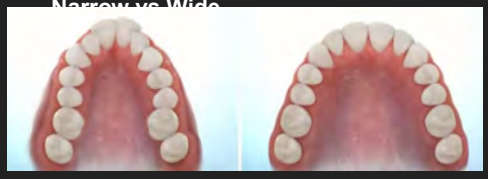
MAXILLARY DEFICIENCY

TEXT



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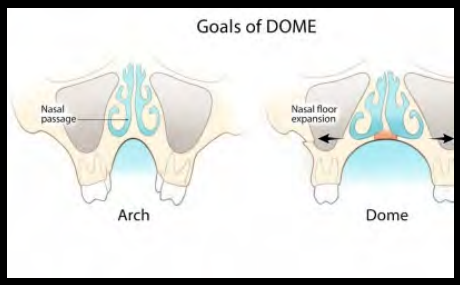

The Impact of Maxillary Expansion on Adults' Nasal Breathing: A Systematic Review and Meta-Analysis

Christian Calvo-Henriquez, MD[1], Joaquim Megias-Barrera, MD, PhD[2], Carlos Chiesa-Estomba, MD MS[3,4], Jerome R. Lechien, MD, MS, PhD[3,5], Byron Maldonado Alvarado, MD[1,3], Badr Ibrahim, MD[3,6], David Suarez-Quintanilla, MD, DDS, PhD[7,8], Sandra Kahn, DDS[9] and Robson Capasso, MD, PhD[6]

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Maxillary expansion in adults

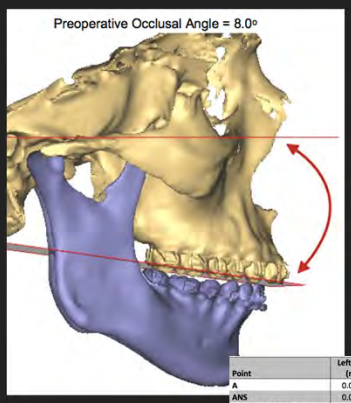
Distraction osteogenesis maxillary expansion (DOME)

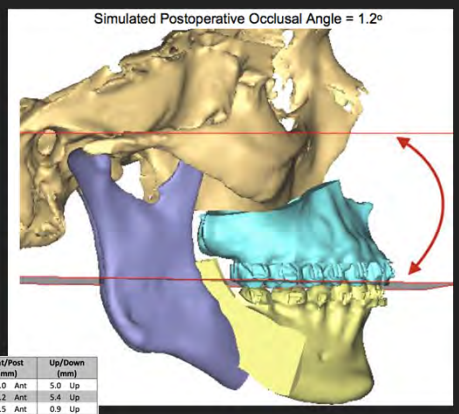
Microimplant assisted Rapid Palatal Expansion (MARPE)

26

TEXT

advancement and counterclockwise rotation





Point	Left/Right (mm)		Ant/Post (mm)		Up/Down (mm)	
A	0.0		5.0	Ant	5.0	Up
ANS	0.0		4.2	Ant	5.4	Up
Maxilla 1st Molar L	0.0		8.5	Ant	0.9	Up
Maxilla 1st Molar R	0.0		7.9	Ant	0.9	Up
Maxilla 2nd Molar L	0.0		8.2	Ant	1.0	Down
Maxilla 2nd Molar R	0.0		7.5	Ant	0.9	Down
Maxilla Canine L	0.0		8.8	Ant	4.7	Up
Maxilla Canine R	0.0		8.4	Ant	4.5	Up
Maxilla Incisor Midline	0.0		8.7	Ant	6.3	Up
B	0.4	R	11.9	Ant	5.9	Up
Mandible 1st Molar L	0.6	R	8.5	Ant	1.3	Up
Mandible 1st Molar R	0.6	R	8.5	Ant	1.2	Up
Mandible 2nd Molar L	0.7	R	8.1	Ant	1.2	Down
Mandible 2nd Molar R	0.7	R	7.9	Ant	1.2	Down
Mandible Canine L	0.4	R	8.3	Ant	5.7	Up
Mandible Canine R	0.4	R	8.1	Ant	5.6	Up
Mandible Incisor Midline	0.4	R	7.9	Ant	6.3	Up
Me	0.5	R	17.2	Ant	4.6	Up
Pog	0.4	R	15.6	Ant	6.1	Up

27

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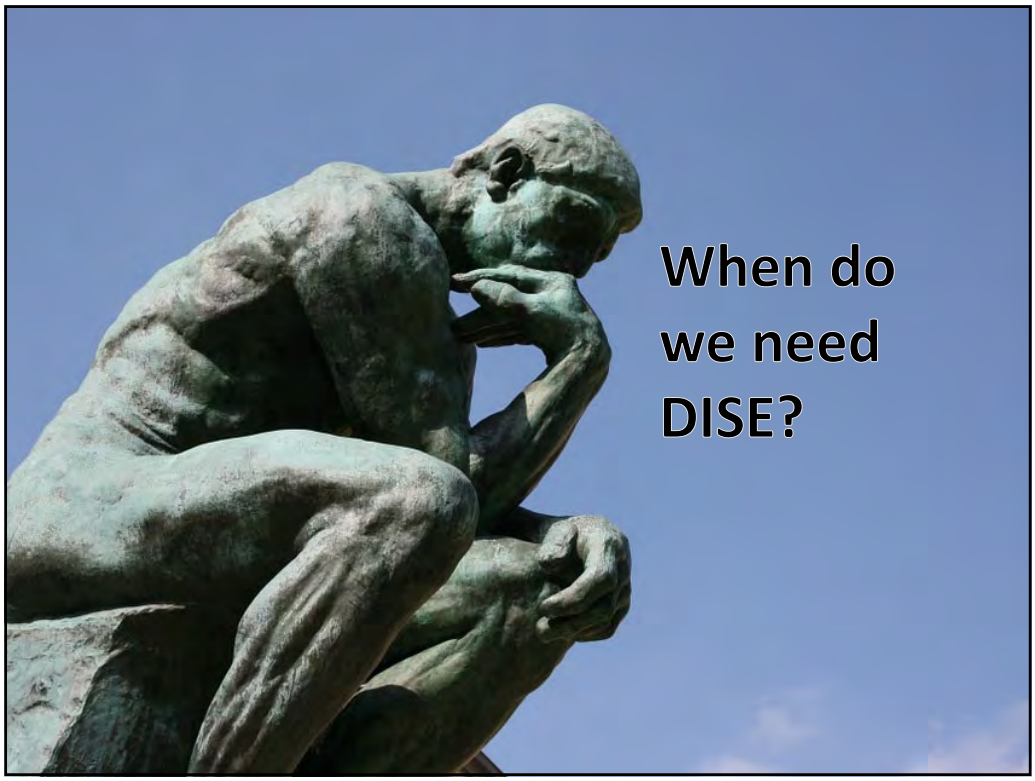

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Lateral Pharyngeal Wall Collapse Associated With Hypoxemia in Obstructive Sleep Apnea

Ming-Chin Lan, MD; Stanley Y. C. Liu, MD, DDS; Ming-Ying Lan, MD, PhD; Rahul Modi, MS, DNB; Robson Capasso, MD, FAASM

The Effect of Aging on Drug-Induced Sleep Endoscopy Findings

Chen Zhao, MD, PhD; Alonço Viana Jr., MD; Yifei Ma, MS; Robson Capasso, MD

Variable Findings for Drug-Induced Sleep Endoscopy in Obstructive Sleep Apnea with Propofol versus Dexmedetomidine

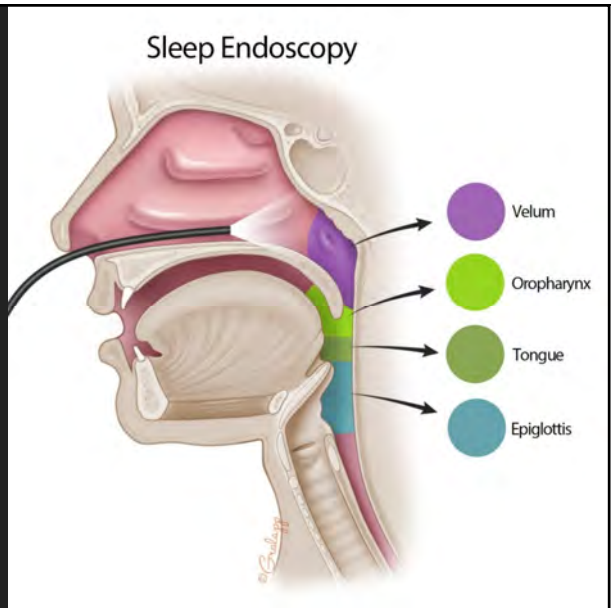
Robson Capasso, MD[1], Talita Rosa, MD[1], David Yung-An Tsou, MD[1,2], Vladimir Nekhendzy, MD[3], David Drover, MD[3], Jeremy Collins, MD[3], Soroush Zaghi, MD[1], and Macario Camacho, MD[4,5]

The Effect of Sedating Agents on Drug-Induced Sleep Endoscopy Findings

Alonço Viana, MD, MSc; Chen Zhao, MD, PhD; Talita Rosa, MD; Arnaldo Couto, PD, PhD; Denise Duprat Neves, MD, PhD; Maria Helena Araújo-Melo, MD, PhD; Robson Capasso, MD

Palatopharyngoplasty Resolves Concentric Collapse in Patients Ineligible for Upper Airway Stimulation

Stanley Yung-Chuan Liu, MD, DDS; Michael J Hutz, MD; Suzukren Promkonsaen, MD; Corissa P Chung, DDS; Michael Awad, MD, FRCSC; Robson Capasso, MD, AIBSM



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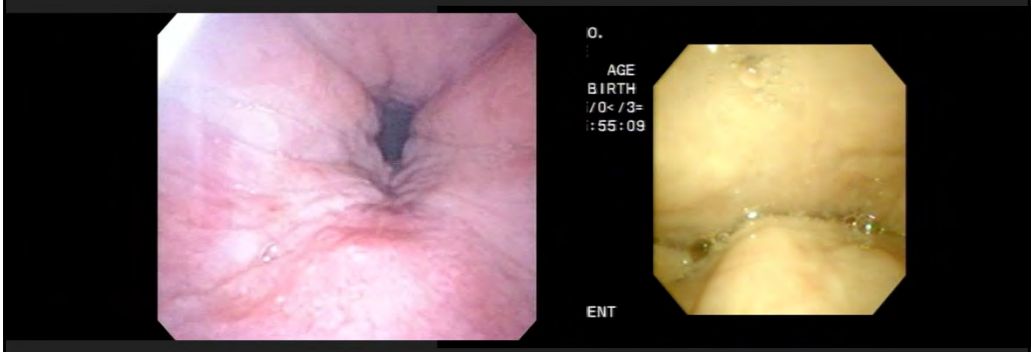
TEXT

When?



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MMA FAILS TOO

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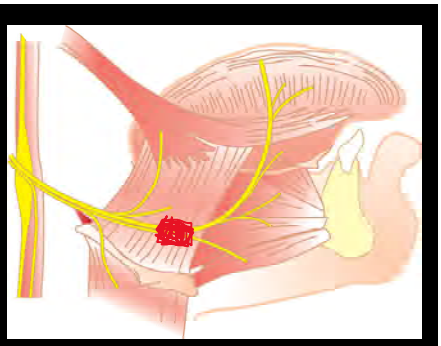
Upper Airway Stimulation



Neurostimulation (currently branches of 12TH cranial nerve, C1)

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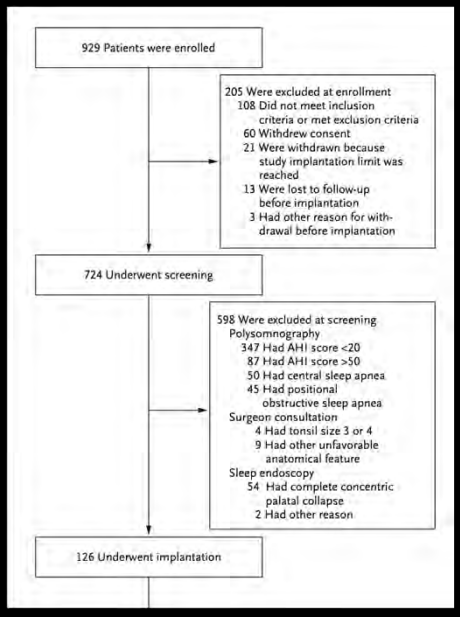

Table 1. Characteristics of the Study Population at Baseline.*

Characteristic	Participants (N = 126)
Age — yr	54.5±10.2
Male sex — no. (%)	105 (83)
White race — no. (%)†	122 (97)
Body-mass index‡	28.4±2.6
Neck size — cm	41.2±3.2
Blood pressure — mm Hg	
Systolic	128.7±16.1
Diastolic	81.5±9.7
Hypertension — no. (%)	48 (38)
Diabetes — no. (%)	11 (9)
Asthma — no. (%)	6 (5)
Congestive heart failure — no. (%)	2 (2)
Uvulopalatopharyngoplasty — no. (%)	22 (17)

* Plus–minus values are means ±SD.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

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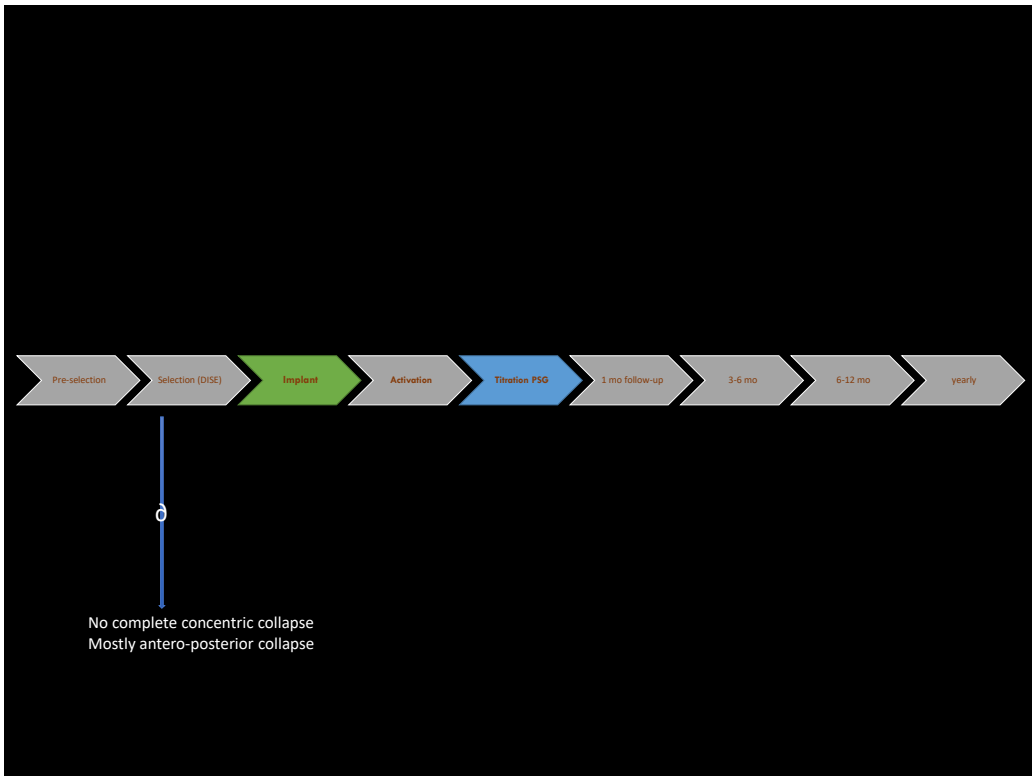

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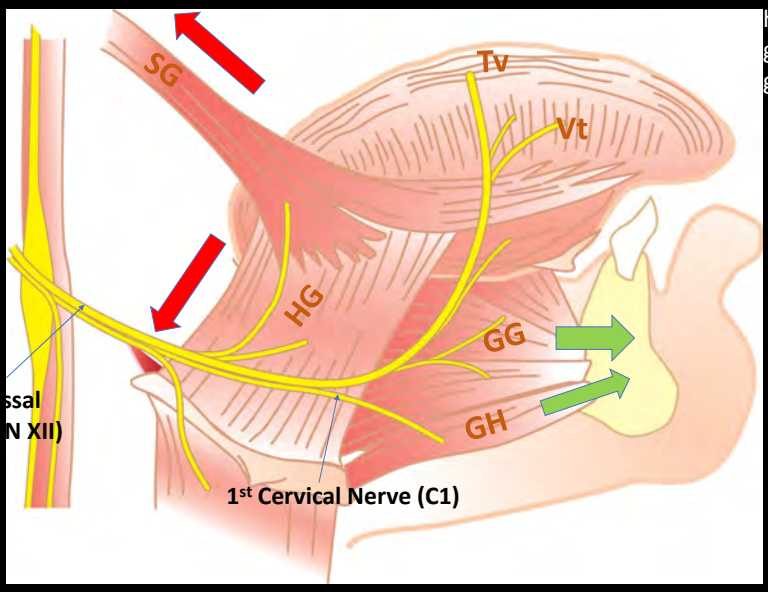
Incisions

- Two incisions

36

SG: styloglossus
Tv: transverse
Vt: vertical
hyoglossus
genioglossus
geniohyoid



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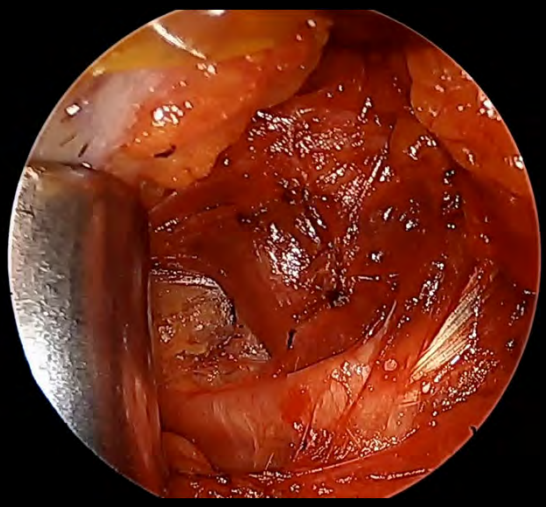
Landmarks



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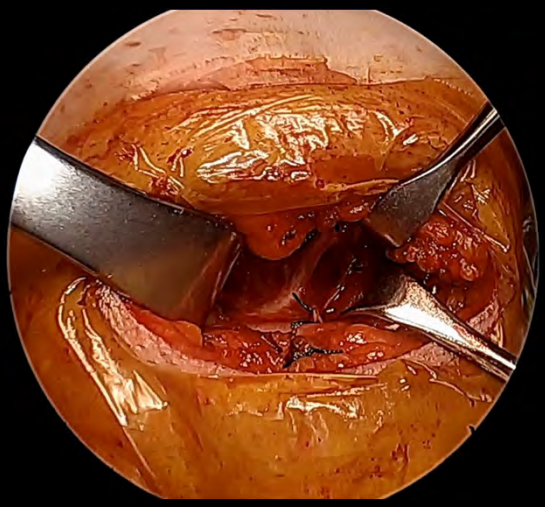
Branch Identification



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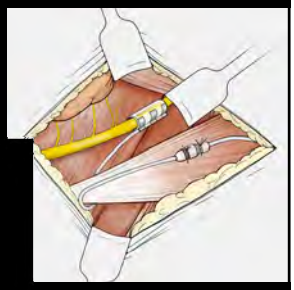
Placement



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Checking

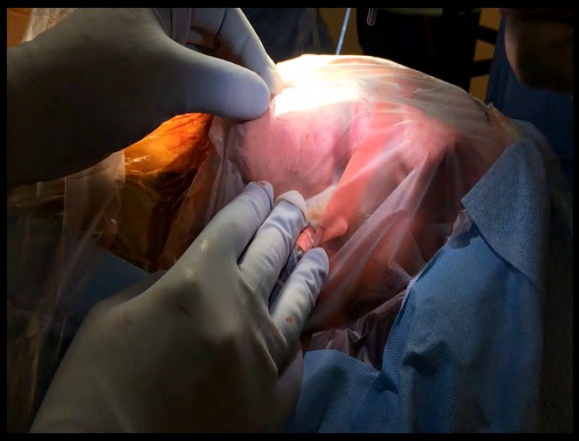

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Table 2. Primary and Secondary Outcome Measures.*

Outcome	Baseline	12 Months	Change	P Value
Primary outcomes				
AHI score†	32.0±11.8	15.3±16.1	−16.4±16.7	<0.001
Median	29.3	9.0	−17.3	
Interquartile range	23.7 to 38.6	4.2 to 22.5	−26.4 to −9.3	
ODI score‡	28.9±12.0	13.9±15.7	−14.6±15.8	<0.001
Median	25.4	7.4	−15.7	
Interquartile range	19.5 to 36.6	3.5 to 20.5	−24.0 to −8.6	
Secondary outcomes				
FOSQ score§	14.3±3.2	17.3±2.9	2.9±3.1	<0.001
Median	14.6	18.2	2.4	
Interquartile range	12.1 to 17.1	16.2 to 19.5	0.7 to 4.7	
Epworth Sleepiness Scale score¶	11.6±5.0	7.0±4.2	−4.7±5.0	<0.001
Median	11.0	6.0	−4.0	
Interquartile range	8.0 to 15.0	4.0 to 10.0	−8.0 to −1.0	
Percentage of sleep time with oxygen saturation <90%	8.7±10.2	5.9±12.4	−2.5±11.1	0.01
Median	5.4	0.9	−2.2	
Interquartile range	2.1 to 10.9	0.2 to 5.2	−6.6 to −0.3	

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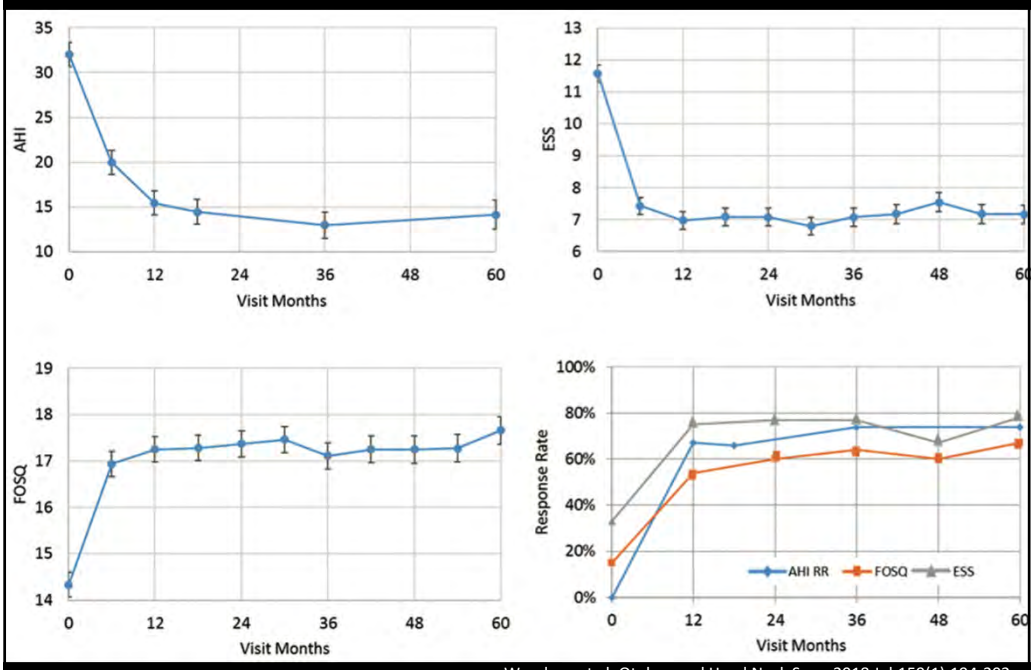
5 YEAR DATA – Positive Outcomes (means/SD)



Woodson et al, Otolaryngol Head Neck Surg. 2018 Jul;159(1):194-202

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Serious AE (n = **8/126**)

- 4 inadequate sensing lead implantation
- 1 unfavorable tongue movement
- 1 reported excessive discomfort
- 1 lead cut off accidentally

Nonserious AE

- 81 **discomfort** due to stimulation at year 1
  - 5 at year 5
- 28 **tongue abrasion** at year 1
  - 2 at year 5

Serious = requiring re-intervention

5 YEAR DATA – Adverse Outcomes

Woodson et al, Otolaryngol Head Neck Surg. 2018 Jul;159(1):194-202

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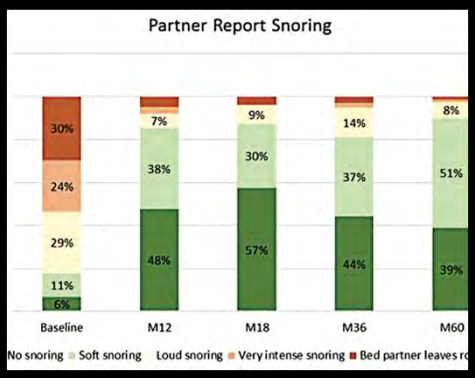
5 YEAR DATA – Adherence, Snoring, Predictors of response

- **# Adherence** (7/7 nights): 86% (1 yr) => 81% (3 yr) => 80% (5 yr)



- **# Predictor** of 5-year sustained response: lower baseline **ODI**

Woodson et al, Otolaryngol Head Neck Surg. 2018 Jul;159(1):194-202

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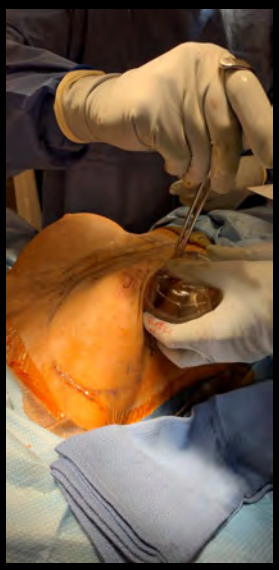
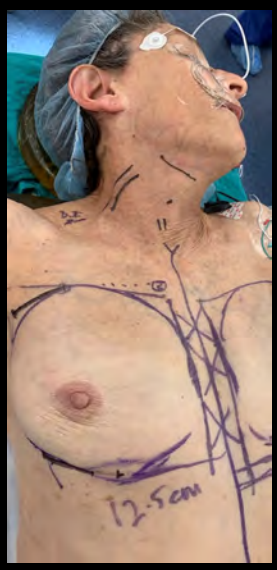
Some challenging…





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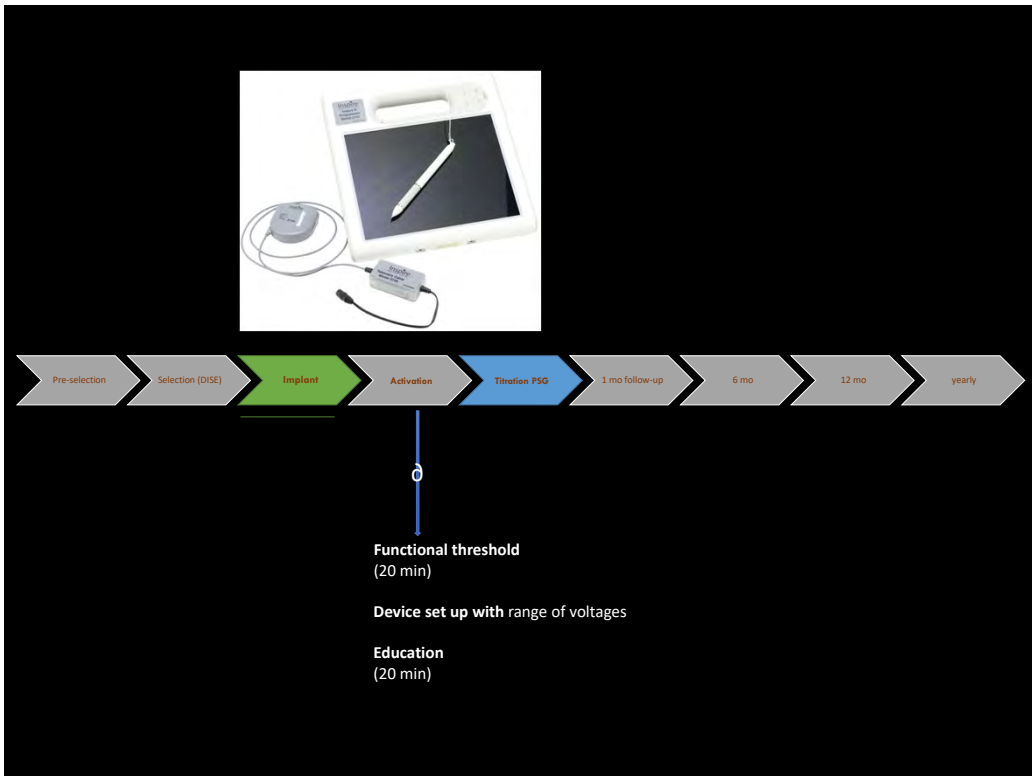
Pre-selection
Selection (DISE)
Implant
Activation
Titration PSG
1 mo follow-up
6 mo
12 mo
yearly
Functional threshold
(20 min)
Device set up with range of voltages
Education
(20 min)

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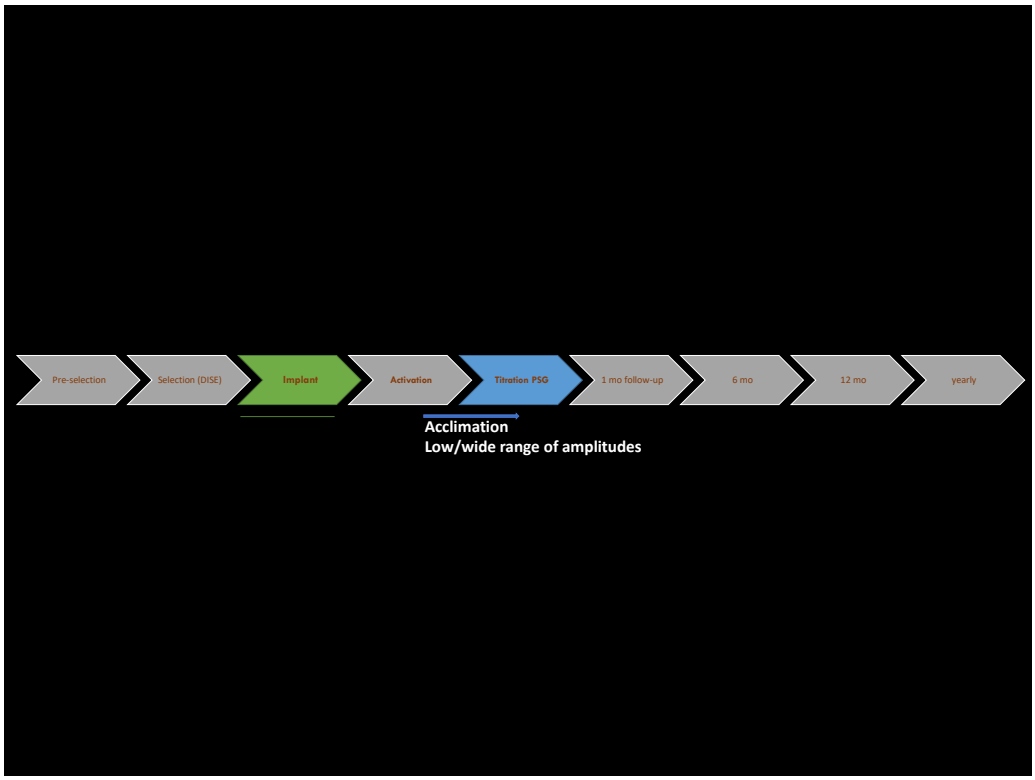
Pre-selection
Selection (DISE)
Implant
Activation
Titration PSG
1 mo follow-up
6 mo
12 mo
yearly
Acclimation
Low/wide range of amplitudes

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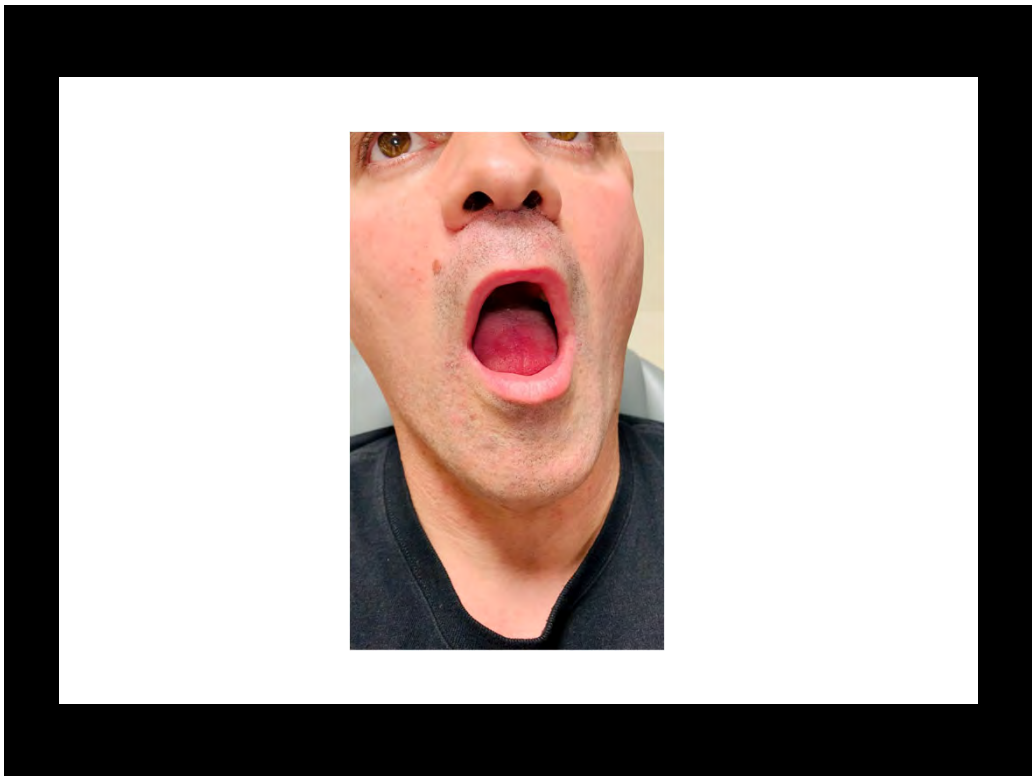

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BMI

- UK National Bariatric Surgery Registry (NBSR): primary bariatric surgery between January 2009 and June 2017.
  - 4015 patients, mean BMI of 51, 60% "remission"
- Upper airway surgery or other therapies are less efficacious in subjects with BMI>37

- Surgery Obes Rel Dis 2021 Sep;17(9):1576-1582.

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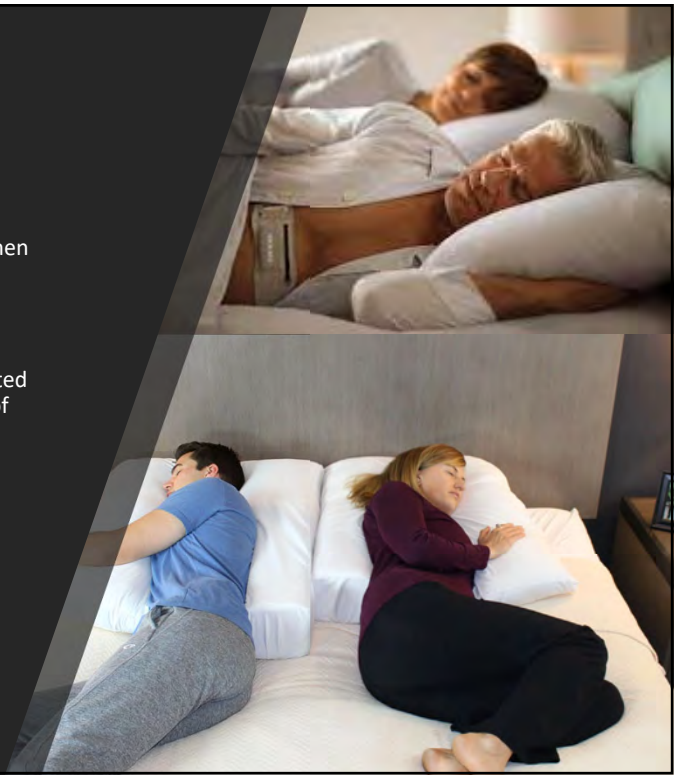
Positional

- Add positional therapy when significant supine component.
- Surgery/UAS/OAT associated with a greater reduction of the non-supine AHI than supine AHI



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Conclusion

- Define the “why” clearly, if CPAP is not an option.
  - AHI is not it, ODI may be best
  - Sleepiness better than fatigue
  - “Must” x “Nice” to treat
  - Consider carefully risks x benefits
- Always discuss:
  - Positional therapy
  - Taper benzos, opioids, muscle relaxants.
- Age, BMI, upper airway and facial skeletal anatomy are key.

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Type of surgery?

The Role of the Revised Stanford Protocol in Today’s Precision Medicine

Stanley Yung-Chuan Liu, MD, DDS*,
Michael Awad, MD, FRCSC, Robert Riley, MD, DDS,
Robson Capasso, MD

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Thank you

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Advances in Pharmacotherapy for Disorders of Hypersomnia

9:50 a.m. – 10:35 a.m.

GAURAV SINGH, MD, MPH
VA PALO ALTO HEALTH CARE SYSTEM
STANFORD UNIVERSITY

Dr. Gaurav Singh received his medical degree from UCSF and completed a Masters of Public Health at UC Berkeley. Currently, he is a Staff Physician at the VA Palo Alto Health Care System in the Section of Pulmonary, Critical Care, and Sleep Medicine. He is also an Affiliated Clinical Assistant Professor at Stanford University, where he completed training in Internal Medicine, followed by Pulmonary and Critical Care fellowship as well as Sleep Medicine fellowship. Dr. Singh has been involved with CTS since 2018 and has been a speaker for the Northern California Annual Conferences in 2019 and 2020. He served on the planning committee for the cancelled CTS Northern California Annual Conference in 2021. He is Conference Co-Chair for the 2022 CTS Annual Educational Conference.

CALIFORNIA THORACIC SOCIETY
A chapter of the American Thoracic Society

ADVANCES IN PHARMACOTHERAPY FOR DISORDERS OF HYPERSOMNIA

Gaurav Singh, MD, MPH
VA Palo Alto Health Care System Staff Physician
Stanford University Affiliated Clinical Assistant Professor
Pulmonary, Critical Care, Sleep Medicine

1

Disclosures

- No financial conflicts
- No conflicts/disclosures

2

Learning Objectives

- Evaluate hypersomnia conditions treated with new pharmacotherapies
- Describe indications for new pharmacotherapies
- Describe contraindications and side effects of new pharmacotherapies
- Discuss management of residual excessive sleepiness in patients with Obstructive Sleep Apnea (OSA)

3

What is Hypersomnia?

- Daytime sleepiness = inability to stay awake/alert during the major waking periods → irrepressible sleepiness or unintended lapses into drowsiness or sleep, for at least 3 months
- Hypersomnolence = chronic daily excessive daytime sleepiness (EDS) despite normal sleep
- Hypersomnia = specific disorders with primary complaint of EDS not due to sleep deprivation, other untreated sleep disorders, etc.

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Hypersomnia vs. Sleep Deprivation vs. Insomnia

	Hypersomnia	Sleep Deprivation	Insomnia
Sleep Opportunity	Adequate/Increased	Reduced	Adequate
Sleep Ability	Adequate	Adequate	Reduced

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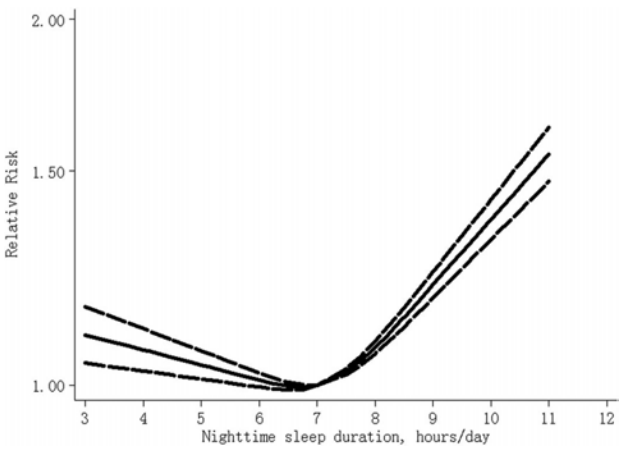
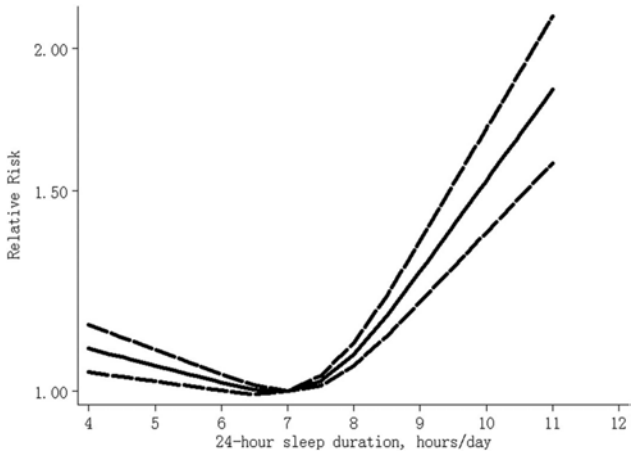
Why Does it Matter?



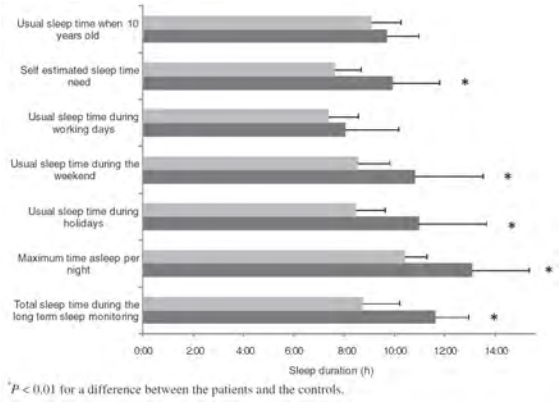


Shen et al. Sci Rep. 2016 Feb 22;6:21480.

6

What Does Hypersomnia Feel Like?

- Daily EDS
- Sleep inertia, sleep drunkenness
- Need for multiple alarms
- Excessive sleep durations, daily naps
- Poor memory, forgetfulness
- Attention deficit
- Confusion, mistakes in habitual activity
- Brain fog, mind going blank

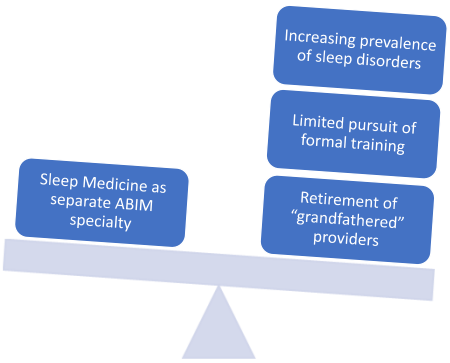


"Modafinil is like botulinum toxin, it keeps my eyes open, but my mind is still asleep"

Vernet et al. J Sleep Res. 2010 Dec;19(4):525-34.

7

Why Should Pulmonologists Care?

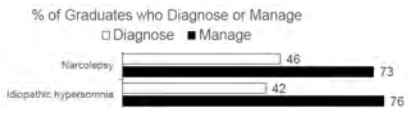


<u>Pulmonary/Critical Care Fellows should:</u>

19.3 Demonstrate knowledge of the history and physical examination needed to identify patients who require formal evaluation for narcolepsy and idiopathic hypersomnia.

21.1 Demonstrate knowledge of the ability to read and interpret a report containing multiple sleep latency test (MSLT) results (secondary interpretation).

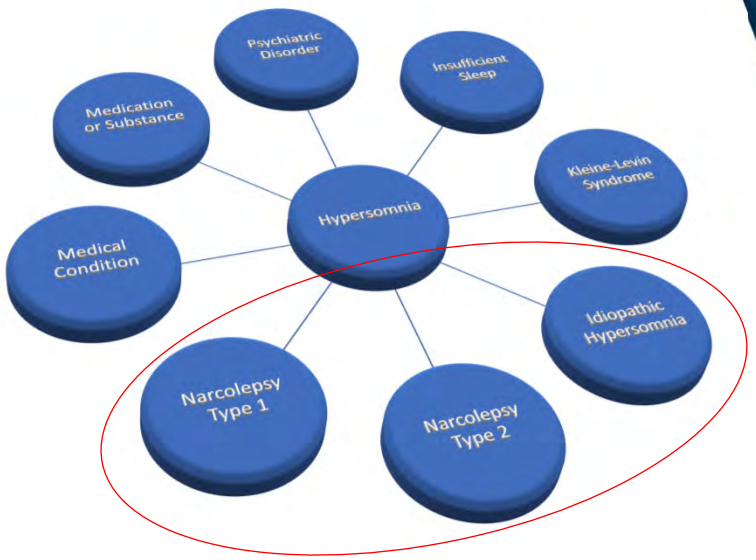
22.1 Demonstrate knowledge of the ability to read and interpret a report containing maintenance of wakefulness test (MWT) results (secondary interpretation).



Schulman et al. Chest. 2019 Mar;155(3):554-564.

8

ICSD-3 Disorders of Hypersomnia



Residual EDS despite treatment for OSA

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Narcolepsy

- EDS
- Cataplexy (Type I and **NOT** II)
- Sleep paralysis
- Sleep hallucinations
- Disrupted nighttime sleep

The Nightmare, by John Fuseli, 1781

Type I: EDS ≥ 3 mo + cataplexy + mean SOL ≤ 8 min with ≥ 2 SOREMPs on MSLT **OR** CSF Hypocretin-1 ≤ 110 pg/ml or <1/3 normal

Type II: EDS ≥ 3 mo + NO cataplexy + mean SOL ≤ 8 min with ≥ 2 SOREMPs on MSLT

CSF Hypocretin-1 > 110 pg/ml if measured

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Narcolepsy Type I vs. Type II

	Narcolepsy Type 1	Narcolepsy Type 2
Prevalence	Higher (1:2000 in US)	Lower (15-25% of cases)
Age of onset	Younger (2nd or 3rd decade)	Older
Cataplexy	Present	Absent
Sleepiness	More	Less
Sleep hallucinations, paralysis, disturbance	More common	Less common
MSLT SOL	Shorter (~ 3 min)	Longer
MSLT SOREMPs	More	Fewer
PSG REM latency	Shorter	Longer
HLA DQB1*0602	90-95%	40%
CSF Hypocretin-1	≤ 110 pg/ml	> 110 pg/ml

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Idiopathic Hypersomnia

EDS ≥ 3 mo + NO cataplexy + ≤ 2 SOREMPs on MSLT + mean SOL ≤ 8 min on MSLT **OR** Total sleep time ≥ 660 min

+ r/o insufficient sleep + Hypersomnolence/MSLT not better explained by other disorder

- Unknown etiology, association with head trauma, symptom onset usually 2nd to 4th decade, spontaneous remission in ~10%
- Other features: severe and prolonged sleep inertia/sleep drunkenness, long and unrefreshing naps, high sleep efficiency (≥ 90%), poor response to treatment

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Narcolepsy vs. Idiopathic Hypersomnia

	Narcolepsy	Idiopathic Hypersomnia
Cataplexy	May be present (type I)	Absent
Sleep paralysis and sleep hallucinations	May be present (type I > II)	May be present
Daytime napping	Transiently refreshing	Not refreshing
Daytime sleepiness	Intermittent	Continuous
Nighttime sleep	Sleep disturbance common ↓ SOL, ↓ REM SL	May be normal or prolonged in duration
MSLT	↓ SOL SOREMPs present (≥ 2)	↓ SOL SOREMPs possible (< 2)
HLA typing	DQB1*0602	CW2
CSF hypocretin	Low levels (type I) Normal levels (type II)	Normal levels
Response to stimulants	More predictable	Less predictable
Remission	No	Possible (~10%)

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MSLT vs. MWT

	MSLT	MWT
Indications	Objective measure of sleepiness	Objective measure of wakefulness
Conditions evaluated	Narcolepsy, idiopathic hypersomnia	Assess level of alertness after treatment of sleep disorders (rarely used)
Number of naps	4 or 5 (in 2-hour intervals)	4 (in 2 -hour intervals)
Duration of naps	20 min (+15 min after sleep onset)	40 min
Instructions	Try to fall asleep while lying in bed in a dark room	Try to stay awake while sitting up in bed with dim light behind the patient, do not do activities to force wakefulness
Interpretation	Mean SOL ≤ 8 min consistent with EDS 0-1 SOREMPs: idiopathic hypersomnia ≥ 2 SOREMPs: narcolepsy	Mean SOL ≤ 8 min: abnormal Mean SOL ≥ 40 min: normal Mean SOL 8-40 min: unclear
Other	Perform immediately after overnight PSG ensuring 6 hours of sleep and excluding OSA; consider actigraphy or use a sleep log for 1-2 weeks prior; hold stimulants, sedatives, hypnotics, REM suppressants for ≥ 2 wk, urine drug screen on day of test, beware of false positives and negatives	

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Subjective Measure of Sleepiness

Epworth Sleepiness Scale (ESS)						
0 Never doze	1 Slight chance	2 Moderate chance	3 High chance			
Sitting and reading			0	1	2	3
Watching television			0	1	2	3
Sitting inactive in a public space			0	1	2	3
As a passenger in a car for an hour without a break			0	1	2	3
Lying down to rest in the afternoon when circumstances permit			0	1	2	3
Sitting and talking to someone			0	1	2	3
Sitting quietly after lunch without alcohol			0	1	2	3
In a car, while stopped for a few minutes in traffic			0	1	2	3
Total Score:						

Score	Interpretation
0-5	Lower normal daytime sleepiness
6-10	Higher normal daytime sleepiness
11-12	Mild excessive daytime sleepiness
13-15	Moderate excessive daytime sleepiness
16-24	Severe excessive daytime sleepiness

Lam et al. J Clin Sleep Med. 2017 Aug 15;13(8):949-957.

Johns. Sleep. 1991 Dec;14(6):540-5.

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Non-Pharmacologic Approaches

Optimize sleep hygiene
- Regular sleep schedule
- Adequate nocturnal sleep
- Brief, scheduled naps (1-3) for narcolepsy
- Avoid shift work
- Exercise

Safety Measures
- Avoid alcohol and other sedative agents
- Caution with driving and operating heavy machinery until EDS controlled

Treat concomitant sleep disorders
- OSA often coexists with narcolepsy
- Weight gain common in narcolepsy
- Oxybates may worsen untreated OSA

Patient and family education
- Symptoms and impact on work & relationships
- Support groups
- Narcolepsy Association

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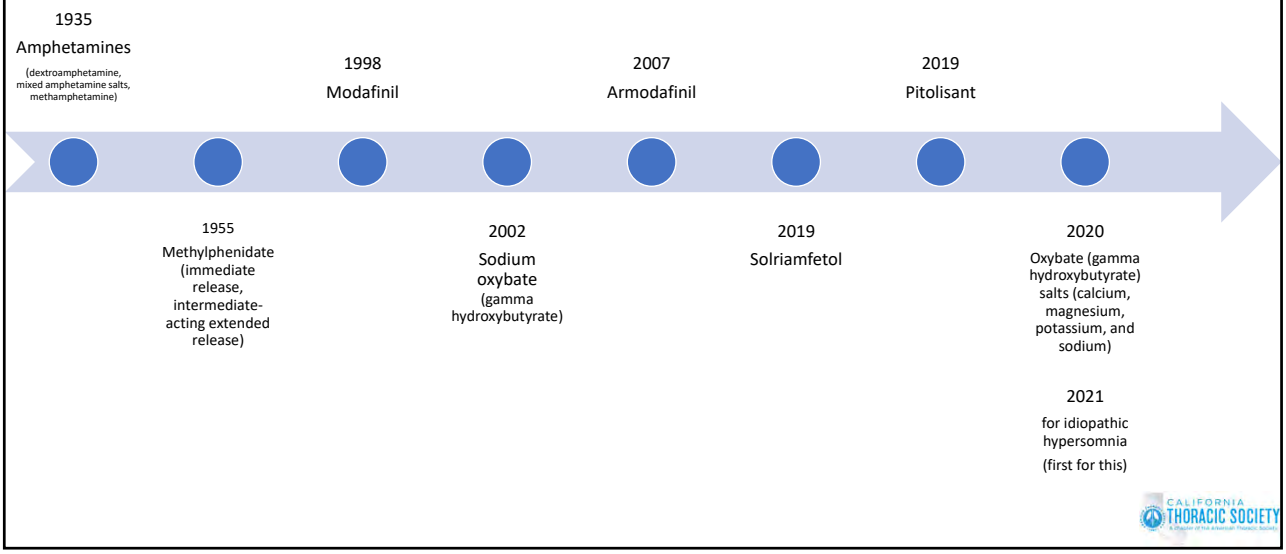
Timeline of FDA Approved Pharmacotherapies



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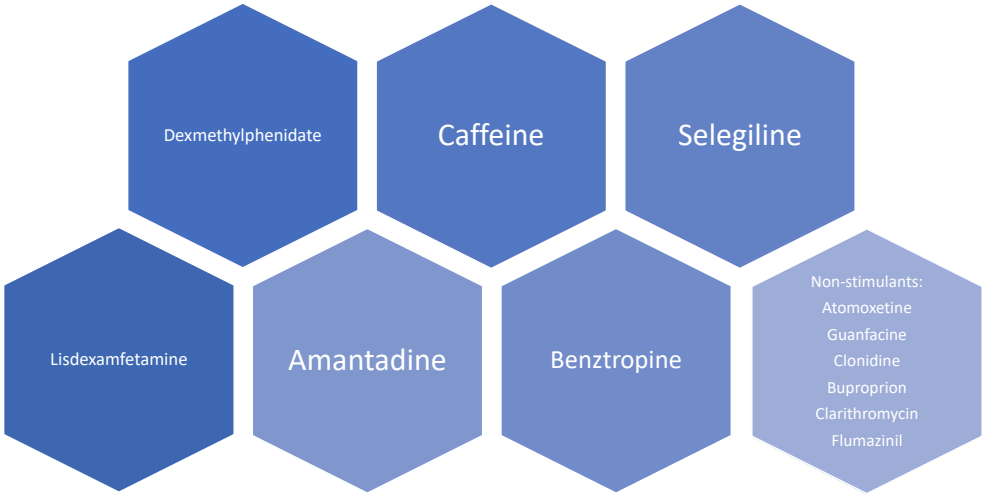
Other Medications



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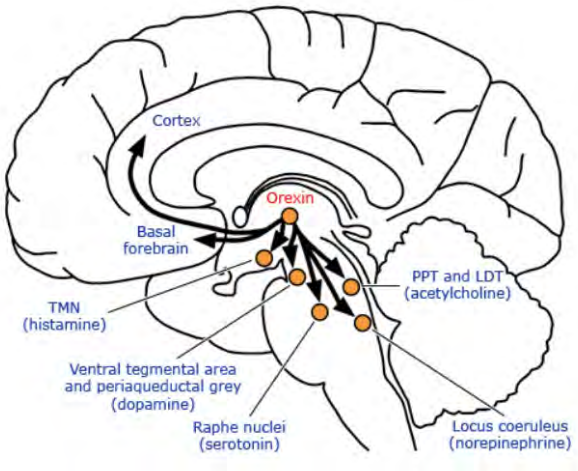
Sleep Neurotransmitters

Neurotransmitter	Sleep	Wake
Adenosine	√	
GABA	√	
Galanin	√	
Glycine	√	
Melatonin	√	
Acetylcholine		√
Dopamine		√
Glutamate		√
Histamine		√
Norepinephrine		√
Orexin 1 and 2		√
Serotonin		√



www.uptodate.com

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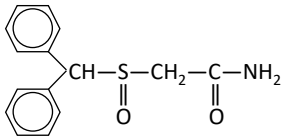
A Moment on Modafinil



Indications	• FDA approved in 1998 (Armodafinil in 2007); approved for narcolepsy, shift work disorder, and residual EDS in OSA
Mechanism	• Oral dopamine reuptake inhibitor, other mechanisms
Dosage	• Modafinil: 100 mg – 400 mg (can divide into 2 doses) • Armodafinil: 150 mg – 250 mg daily
Pharma	• Peak plasma concentration at 2 – 4 hr (fasting) • $t_{1/2}$ of 15 hr
Trials	• 2 RCTs for narcolepsy with improvements in ESS, MWT (n = 554) • 2 RCTs for idiopathic hypersomnia with improvements in ESS, MWT, CGI-C (n = 104) • Multiple RCTs for treatment of residual sleepiness in adequately treated OSA

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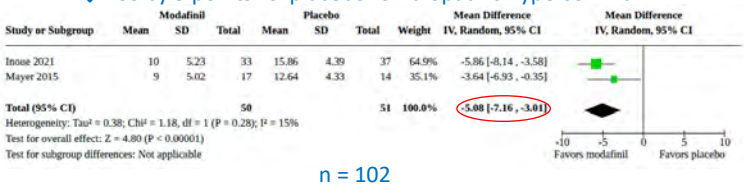
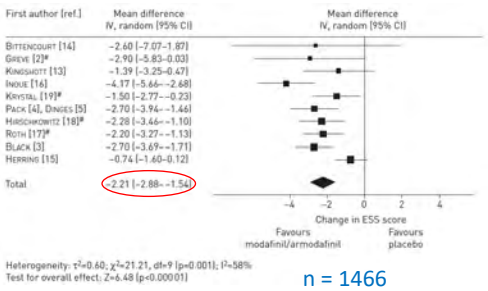
Modafinil: The Evidence

↓ ESS by 5 points vs. placebo for idiopathic hypersomnia



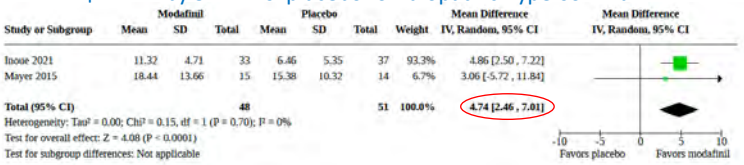
n = 102

↓ ESS by 2 points vs. placebo for OSA

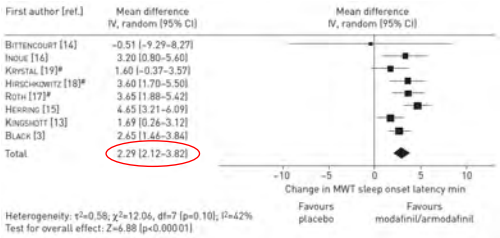


n = 1466

↑ MWT by 5 min vs. placebo for idiopathic hypersomnia



↑ MWT by 3 min vs. placebo for OSA



Trotti et al. Cochrane Database Syst Rev. 2021 May 25;5(5):CD012714.

Chapman et al. Eur Respir J. 2016 May;47(5):1420-8.

21

Modafinil: Safety, Side Effects, and Cautions

Schedule	• Schedule IV controlled substance
Common side effects	• Headache (34%), nausea (11%), dry mouth (4%), anorexia (4%), back pain (6%), anxiety (5%), insomnia (5%), rhinitis, diarrhea (6%) • Possible adverse cardiovascular risk (chest pain, HTN, palpitations)
Serious side effects	• Stevens-Johnson syndrome and toxic epidermal necrolysis, rare cases of multi-organ hypersensitivity reactions, isolated cases of angioedema and anaphylactoid reactions
Renal/hepatic concerns	• Renal excretion • One-half dose for severe hepatic failure (hepatic metabolism)
Other	• Lower potential for abuse vs. other stimulants (e.g. amphetamine derivatives) • Decreases effectiveness of hormonal contraception • Metabolized by CYP3A4

22

New Drugs on the Block

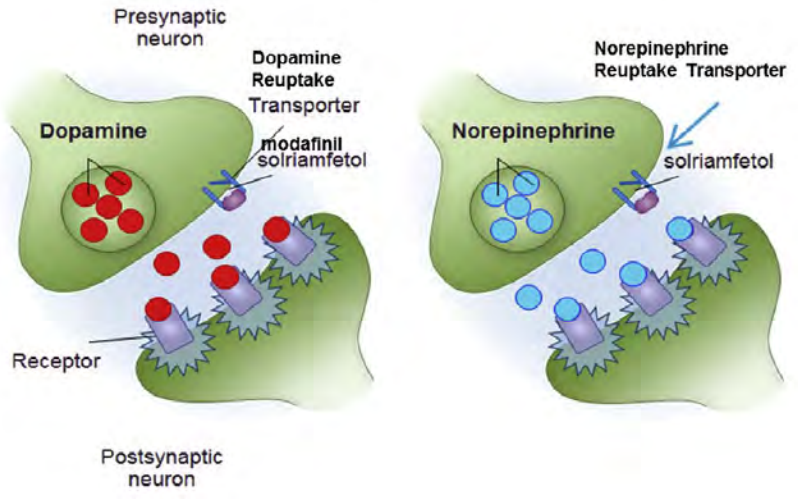
23

Solriamfetol

Indications	• FDA approved in 2019 for narcolepsy and residual EDS in OSA despite therapy (after ≥ 1 month)
Mechanism	• Oral selective dopamine and norepinephrine reuptake inhibitor with wake-promoting effects
Dosage	• Narcolepsy: 75 mg – 150 mg (increase in intervals of ≥ 3 days) • OSA: 37.5 mg – 150 mg (increase in intervals of ≥ 3 days)
Pharma	• Peak plasma concentration at 2 hr (fasting) • $t_{1/2}$ of 7.1 hr
Trials	• TONES 1 and 2: narcolepsy • TONES 3: OSA • TONES 4 and 5: both narcolepsy and OSA, withdrawal trials

24

Solriamfetol: Mechanism

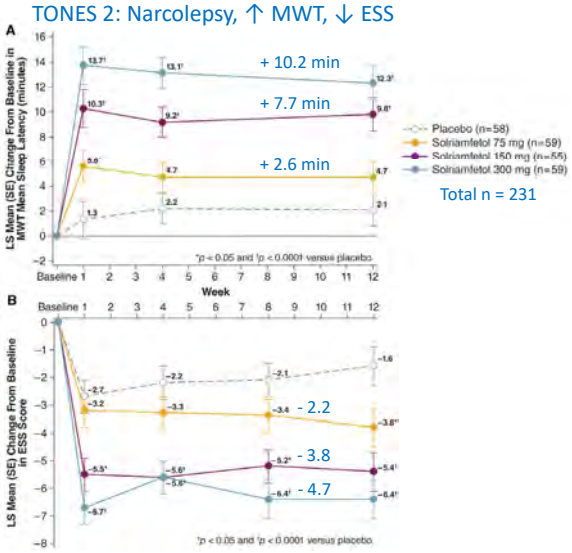


Javaheri and Javaheri. Chest. 2020 Aug;158(2):776-786. (Original Source Jazz Pharmaceuticals)

25

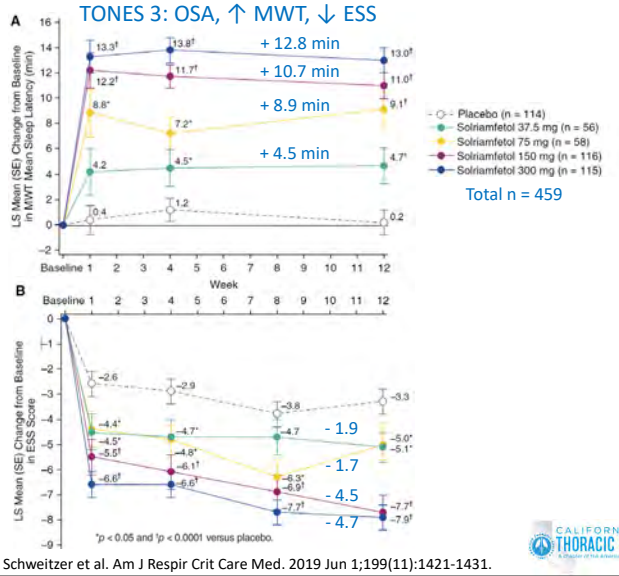
Solriamfetol: The Evidence

TONES 2: Narcolepsy, ↑ MWT, ↓ ESS



Thorpy et al. Ann Neurol. 2019 Mar;85(3):359-370.

TONES 3: OSA, ↑ MWT, ↓ ESS

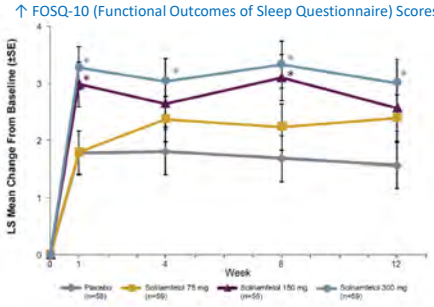


Schweitzer et al. Am J Respir Crit Care Med. 2019 Jun 1;199(11):1421-1431.

26

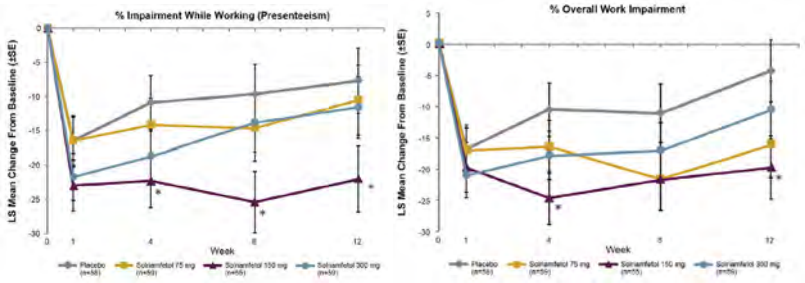
Solriamfetol: Other Outcomes

↑ FOSQ-10 (Functional Outcomes of Sleep Questionnaire) Scores

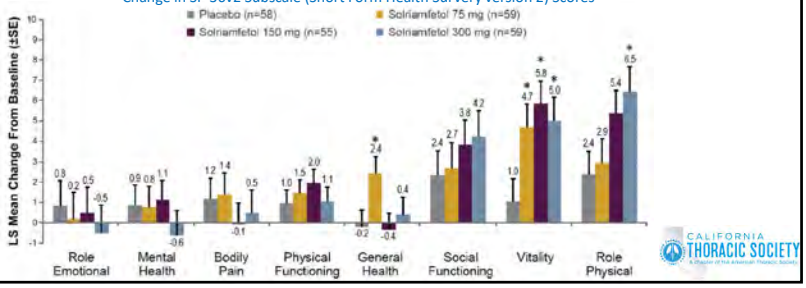


*P < 0.05 vs placebo

Work Productivity and Activity Impairment questionnaire for Specific Health Problem (WPAI:SHP)



Change in SF-36v2 Subscale (Short Form Health Survery version 2) Scores



Emsellem et al. Sleep Med. 2020 Mar;67:128-136.

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Solriamfetol: Safety, Side Effects, & Cautions

Schedule	• Schedule IV controlled substance
Common side effects	• Headache (16%), nausea (7-8%), decreased appetite (6-9%), anxiety (4-6%), insomnia (5%), nasopharyngitis, dry mouth • Take in the morning and not within 9 hr of planned bedtime • Small, dose-dependent increases in mean BP and HR (monitor; 300 mg not approved)
Renal/hepatic concerns	• Renal excretion • Dosing adjustment for renal impairment
Contraindications	• Do not use with MAOIs within 14 days
Other	• Not effective for cataplexy • Does **not** interfere with oral contraceptives (metabolized in liver)

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Pitolisant

Indications	• FDA approved in 2019 for narcolepsy (EDS and cataplexy)
Mechanism	• Oral histamine H3 receptor inverse agonist that improves sleepiness and reduces cataplexy
Dosage	• Start 8.9 mg, increase to 17.8 mg after 1 week if well tolerated • Maximum 35.6 mg (by week 3)
Pharma	• Peak plasma concentration at 3.5 hr • $t_{1/2}$ of 20 hr
Trials	• HARMONY 1: placebo-controlled double-blind phase 3 (2013) • HARMONY CTP: placebo-controlled double-blind phase 3 for cataplexy (2017) • HARMONY III: open-label long-term follow-up (12 mo vs 3 mo; 2019)

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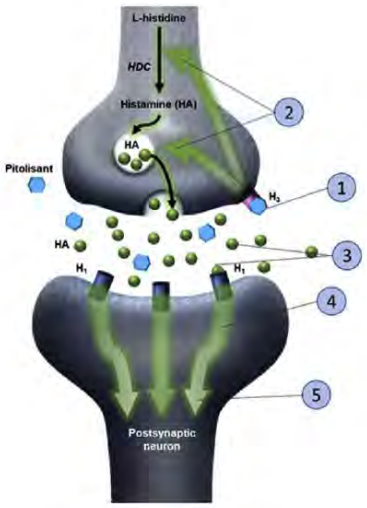
Pitolisant: Mechanism

- Pitolisant is a histamine H_3-receptor antagonist/inverse agonist that enhances the activity of histaminergic neurons in the brain[1-5]
  1. Pitolisant binds to presynaptic H_3 autoreceptors, which blocks histamine binding to these receptors
  2. Acting as an inverse agonist, pitolisant initiates increased histamine synthesis and increased histamine release from vesicles
  3. These two actions result in increased histamine in the synapse, which is then available for binding to excitatory post-synaptic H_1 receptors
  4. Increased histamine binding at H_1 receptors causes in an increase in neuronal firing
  5. Increased firing of histamine neurons causes increased activation of wake-associated brain regions and increased inhibition of non-REM and REM sleep-associated brain regions

HA = histamine; HDC = L-histidine decarboxylase.

Figure adapted from: Benarroch EE. Neurology. 2010;75(16):1472-1479.



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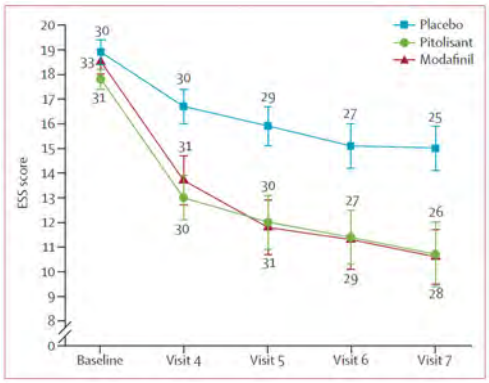
Javaheri and Javaheri. Chest. 2020 Aug;158(2):776-786. (Original Source Benarroch. Neurology. 2010;75(16):1472-1479.)

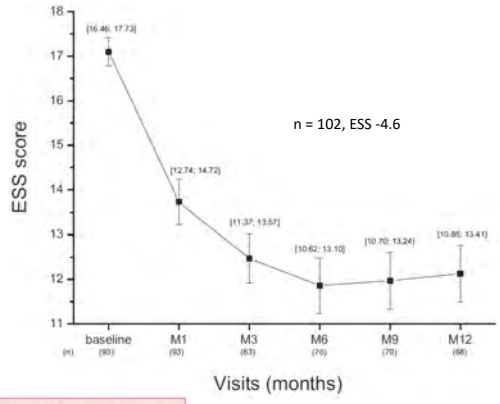
30

Pitolisant: The Evidence



n = 30, ESS - 3.4
n = 32, ESS - 5.8
n = 33, ESS - 6.9
Total n = 95

8 weeks



n = 102, ESS -4.6

	Placebo			Pitolisant			Modafinil			Treatment effect (mean difference [95% CI]; p value)	
	Baseline	Final	Change over trial*	Baseline	Final	Change over trial*	Baseline	Final	Change over trial*	Pitolisant vs placebo (superiority test)	Pitolisant vs modafinil (non-inferiority test)
ESS (primary endpoint; change = final – baseline)	18·9 (2·5)	15·6 (4·3)	−3·4 (4·2)	17·8 (2·5)	12·0 (6·2)	−5·8 (6·2)	18·5 (2·7)	11·6 (6·0)	−6·9 (6·2)	−3·0 (−5·6 to −0·4); p=0·024	0·12 (−2·5 to 2·7); p=0·250
MWT	8·4 (1·8)	7·6 (3·0)	0·88	7·4 (2·3)	9·7 (2·8)	1·32	8·8 (2·5)	15·1 (2·7)	1·72	1·47 (1·01 to 2·14); p=0·044	0·77 (0·52 to 1·13); p=0·173

Dauvilliers et al. Lancet Neurol. 2013 Nov;12(11):1068-75.

Dauvilliers et al. Sleep. 2019 Oct 21;42(11):zsz174.

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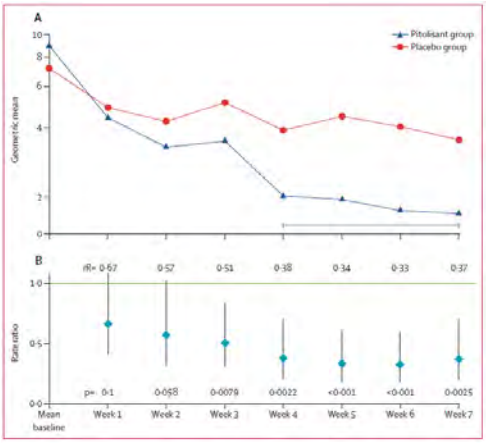
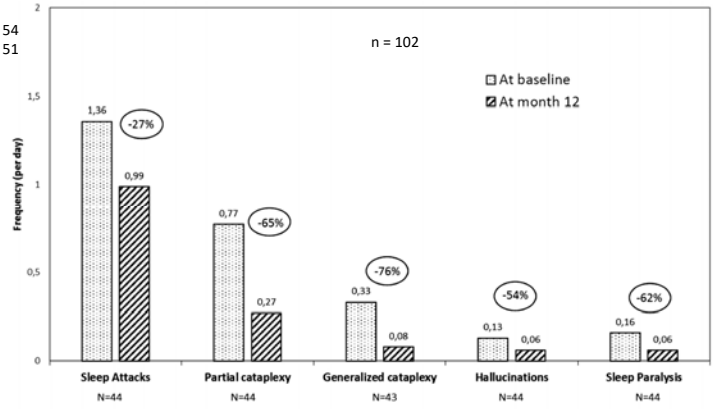
Pitolisant: Other Outcomes

↓ weekly cataplexy rate



n = 54
n = 51



Szakacs et al. Lancet Neurol. 2017 Mar;16(3):200-207.

Dauvilliers et al. Sleep. 2019 Oct 21;42(11):zsz174.

32

Pitolisant: Safety, Side Effects, and Cautions

Schedule	• **Not** scheduled as controlled substance
Common side effects	• Headache (18%), insomnia (6%), nausea (6%), anxiety (5%), abdominal discomfort, irritability, weight gain, depression
Serious side effects	• Rare cases of allergy and anaphylaxis reported • Associated with dose-dependent prolongation of QT interval
Renal/hepatic concerns	• Renal excretion mostly, also hepatic • Dosing adjustment for renal and hepatic impairment
Other	• Decreases effectiveness of hormonal contraception • Interaction with CYP2D6 inhibitors and CYP3A4 inducers

33

Lower-Sodium Oxybate

Indications	• FDA approved in 2020 for narcolepsy (EDS and cataplexy) • 2021 for idiopathic hypersomnia (first drug approved for this)
Mechanism	• Oral liquid gamma hydroxybutyrate (GHB), metabolite of gamma amino butyric acid (GABA), is active moiety of oxybates that acts as $GABA_B$ agonist to induce deep sedation • 90% less sodium that sodium oxybate – use of calcium, magnesium, potassium, sodium oxybates
Dosage	• Narcolepsy/IH: 4.5 g nightly (2 divided doses, 2.5 – 4 hr apart), increase by 1.5 g at weekly intervals (or every 2 – 4 weeks), max 9 g (usual effective dose 6 – 9 g) • Idiopathic hypersomnia: can use twice nightly as above; for once nightly, start ≤ 3 g, increase by ≤ 1.5 g at weekly intervals, maximum 6 g
Pharma	• Peak plasma concentration at 1.3 hr (fasting) • $t_{1/2}$ of 0.66 hr
Trials	• Prior trials of sodium oxybate for narcolepsy • Multicenter placebo-controlled double-blind phase 3 randomized withdrawal study for idiopathic hypersomnia

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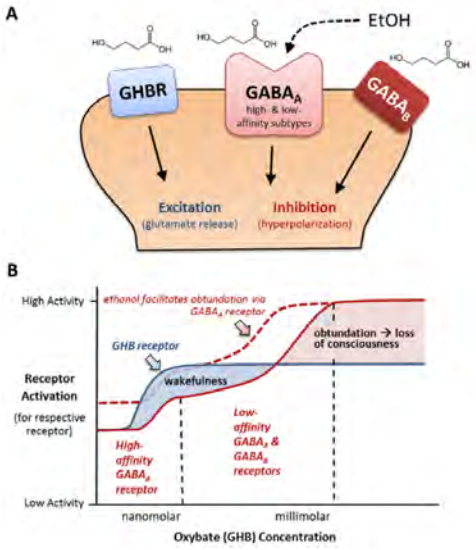
Lower-Sodium Oxybate: Mechanism



VanWert et al. J Pharm Technol. 2014 Dec;30(6):240-243.

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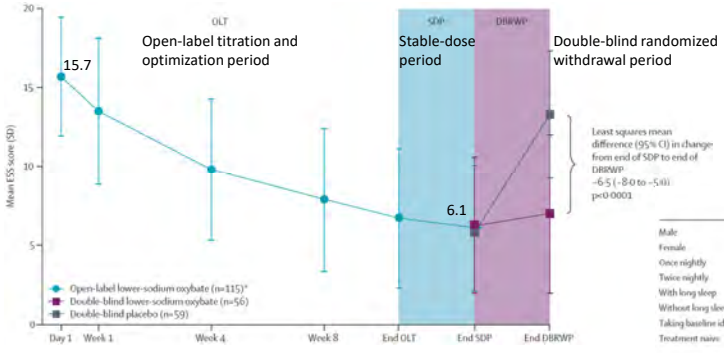
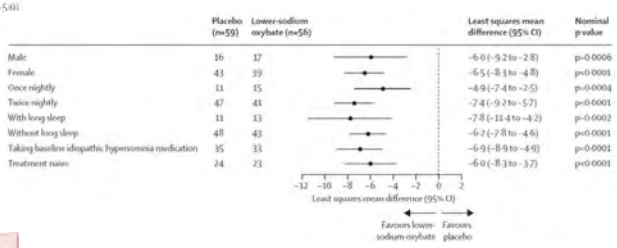
Lower-Sodium Oxybate: The Evidence





	Lower-sodium oxybate group (n=56)			Placebo group (n=59)			Difference between groups	p value
	Baseline	End of SDP	End of DBRWP	Baseline	End of SDP	End of DBRWP		
Primary outcome								
Epworth Sleepiness Scale	15·6 (3·3)	6·3 (4·3)	7·0 (5·0)	15·9 (4·2)	5·8 (3·7)	13·3 (4·1)	Least squares mean difference (95% CI): −6·5 (−8·0 to −5·0)	<0·0001

Dauvilliers et al. Lancet Neurol. 2022 Jan;21(1):53-65.

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Lower-Sodium Oxybate: Safety, Side Effects, Cautions

Schedule	• Schedule III-C controlled substance, REMS Program
Common side effects	• headache (20%), nausea (13%), dizziness (10%), decreased appetite (8%), urinary incontinence, emesis, mood swings, anxiety, worsening of depression, sleepwalking, psychosis
Serious side effects	• Over-dosage can result in respiratory depression, coma, death (Boxed Warning) – combined use with alcohol or sedative hypnotics is contraindicated, caution with CNS depressants
Renal/hepatic concerns	• Reduce dose by 50% for hepatic impairment
Other	• GHB also known as "date rape" drug – potential for abuse

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2021 AASM Guidelines for EDS

Intervention	Strength of Recs	EDS	Disease Severity	Quality of Life
Narcolepsy				
Modafinil	Strong	√	√	√
Pitolisant	Strong	√	√	
Sodium oxybate	Strong	√	√	
Solriamfetol	Strong	√	√	√
Armodafinil	Conditional	√	√	
Dextroamphetamine	Conditional	√		
Methylphenidate	Conditional		√	
Idiopathic Hypersomnia				
Modafinil	Strong	√	√	
Clarithromycin	Conditional	√	√	√
Methylphenidate	Conditional		√	
Pitolisant	Conditional	√		
Sodium oxybate	Conditional	√		

Maski et al. J Clin Sleep Med. 2021 Sep 1;17(9):1881-1893.

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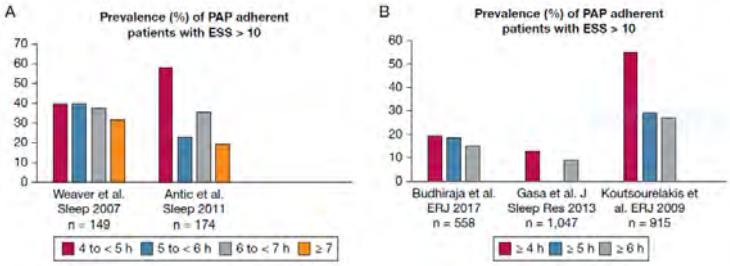
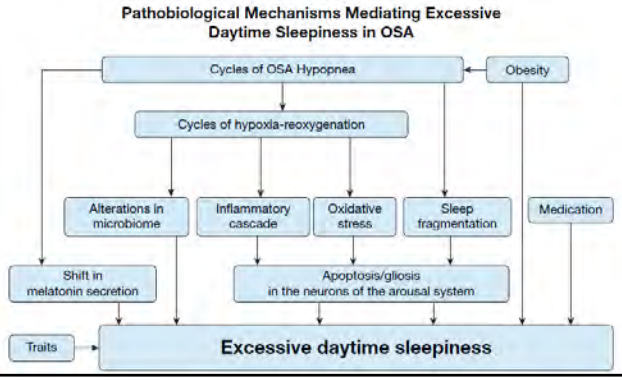
Residual EDS in Treated OSA

- Prevalence 6 – 55%
- Even when treatment adherence, medications, comorbid illness, and inadequate sleep are controlled, prevalence 6-18%
- Associated with higher ESS and lower AHI on presentation, age < 55





Javaheri and Javaheri. Chest. 2020 Aug;158(2):776-786.

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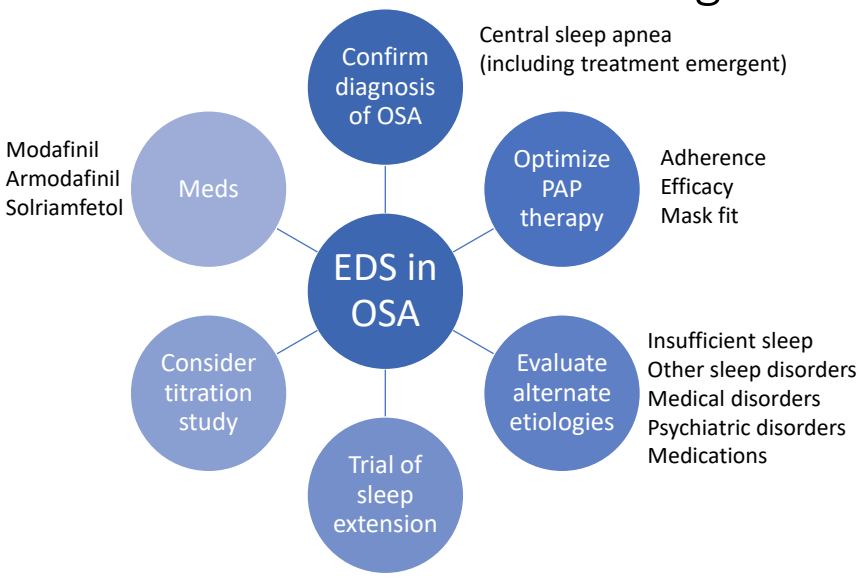
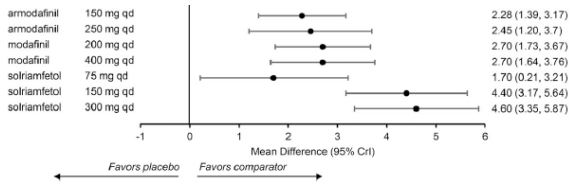
Residual EDS in Treated OSA: Management



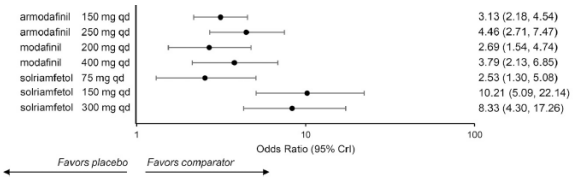
40

Which Medication is the Best for OSA?

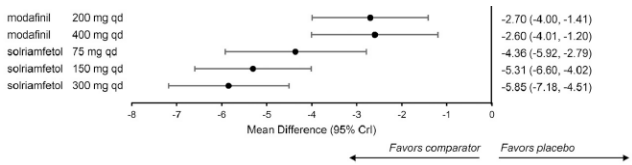
Improvement in ESS vs. placebo after 12 weeks



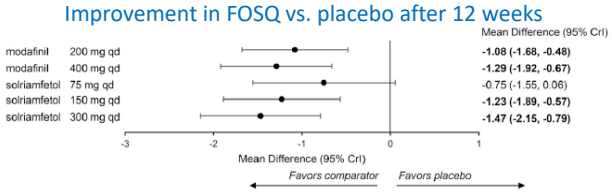
Improvement in CGI-C vs. placebo after 12 weeks



Improvement in MWT at 20 min vs. placebo after 12 weeks



Improvement in FOSQ vs. placebo after 12 weeks



Ronnebaum et al. J Clin Sleep Med. 2021 Dec 1;17(12):2543-2555.

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Summary of Hypersomnia Medications

Medication	Dosage	Indications	Mechanism	Comments
Modafinil	100 – 400 mg (can be in 2 divided doses)	Narcolepsy IH OSA	DA reuptake inhibitor	Less addictive, first-line med, SJS and TEN, caution w/ hormonal contraception
Armodafinil	150 – 250 mg	Narcolepsy IH OSA	DA reuptake inhibitor	Similar to Modafinil, use for EDS in dementia with Lewy bodies
Solriamfetol	Narcolepsy: 75 – 150 mg OSA: 37.5 – 150 mg ↑ ≥ 3 days	Narcolepsy OSA	DA / NE reuptake inhibitor	Monitor BP and HR, renal dosing, not with MAOIs, no other drug interactions, OCPs okay, ?best for OSA
Pitolisant	8.9 – 35.6 mg ↑ ≥ 1 week	Narcolepsy	H3 inverse agonist	Anaphylaxis, renal/hepatic dosing, QT, drug interactions, caution w/ hormonal contraception, not controlled
Oxybates	4.5 – 9 g nightly 2 divided doses (2.5 – 4 hr apart) ↑ 1.5 ≥ 1 week 3 – 6 g once nightly option for IH ↑ 1.5 g ≥ 1 week	Narcolepsy IH	$GABA_B$ agonist	No EtOH or sedative hypnotics (respiratory depression), hepatic dosing, REMS program

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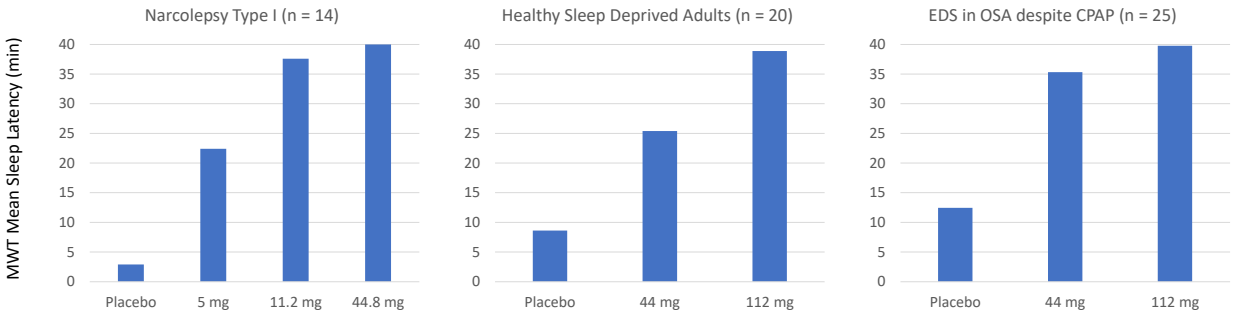
TAK-925 (Orexin 2 Receptor Agonist) Phase Ib Teaser



Evans et al. World Sleep, 2019.

Rubens et al. 73rd Annual Meeting of the American Academy of Neurology (AAN), 2021.

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Take Home Points

- Hypersomnia causes severe functional impairment, associated with increased mortality
- Optimize non-pharmacologic therapies
- The medications available in the last few years that are helpful for narcolepsy, idiopathic hypersomnia, and EDS in treated OSA include Solriamfetol, Pitolisant, and Oxybate salts
- Modafinil remains a primary treatment for these conditions
- Choice of medication is based on experience, efficacy, side effect profile, drug interactions, abuse potential, availability

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Thank You!

CALIFORNIA THORACIC SOCIETY

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BREAK
EXHIBIT HALL OPEN

10:35 a.m. – 10:50 a.m.

Insomnia Management Strategies

10:50 a.m. – 11:35 a.m.

MICHELLE PRIMEAU, MD
SUTTER HEALTH SAN CARLOS

Dr. Michelle Primeau obtained her medical degree from Case Western Reserve University in Cleveland, OH. She completed a residency in Psychiatry, but in her first year found the field of sleep medicine and was enamored. She completed her fellowship in Sleep Medicine at Stanford, as well as a post-doctoral research fellowship in sleep and mental health. In 2014, she came to Sutter Health/Palo Alto Medical Foundation and started the Sleep Wellness Program, integrating a full behavioral sleep medicine program throughout the Bay Area by training MDs, PAs, NPs and LCSWs to perform Cognitive Behavioral Therapy for Insomnia within their departments. Her clinical aim is the holistic approach to sleep medicine, integratingevaluation of lifestyle, circadian influences, as well as other physiologic disorders (OSA, RLS) for achieving sleep wellness.

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A chapter of the American Thoracic Society

Insomnia for the sleep and non-sleep specialist

Michelle Primeau, MD
Palo Alto Medical Foundation
Department of Sleep Medicine

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Disclosures

- Conflict (prior):
  - Consultant: Pear Therapeutics (Somryst)- FDA advisory committee and media
  - Speaker: Merck (Belsomra)
  - No active conflicts to disclose

2

AGENDA

- Review related diagnoses
- Review guidelines
  - CBT-Insomnia
  - Sedative-hypnotic medications
- Goals in prescribing
- What can YOU do?

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MP

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Prevalence

Usually, ~10-20% syndrome, 30% symptoms
- older adults, may be more like 50%

However, with the pandemic, we have been seeing reports of increased insomnia

Conceptualized as Hyperarousal

Table 1. Changes in sleep status from before to during the COVID-19 pandemic (n = 594).

	Time 2 (May 2020)		
Time 1 (2018)	Good sleepers (n = 290)	Subsyndromal insomnia (n = 191)	Insomnia syndrome (n = 113)
Good sleepers (n = 343)	231 (68.5%)	87 (25.6%)	25 (5.9%)
Subsyndromal insomnia (n = 151)	46 (31.3%)	81 (51.4%)	24 (17.3%)
Insomnia syndrome (n = 100)	13 (12.4%)	23 (22.4%)	64 (65.2%)

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Crowley 2011; Morin 2022

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COVID impact on sleep

Change in bedtime, rise time, SE%, naps

- also saw higher fatigue, depression, anxiety

Table 3. Changes in sleep habits from pre- to during the COVID-19 pandemic (n = 594)

	Mean ± standard error		
Variable	Time 1 (2018)	Time 2 (May 2020)	P
Bedtime	22:38 ± 0.1	22:50 ± 0.1	<.0001
Arising time	6:58 ± 0.1	7:16 ± 0.1	<.0001
Sleep duration (hours)	7:18 ± 0.1	7:19 ± 0.1	.8404
Sleep efficiency (%)	88.2 ± 0.7	81.9 ± 0.7	<.0001
Naps (frequency)	1.2 ± 0.1	2.1 ± 0.1	<.0001
Use of sleep medication (%)	13.5 ± 0.0	15.2 ± 0.0	.0983

Isolation predicted insomnia/ depression/ anxiety
Insomnia/ lower sleep quality predicted by:
- Increased use of device
- Increased time in room
- Reduced physical activity
- Financial worries

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Morin 2022

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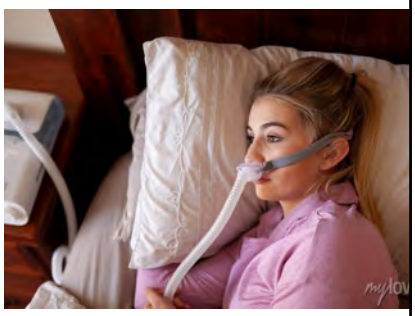
INSOMNIA STATS- WHY SHOULD I CARE?

- Frequently co-morbid with OSA- ~50%
  - Ong and Crawford,2013
  - Insomnia limits adherence to CPAP
  - CBTI improves adherence to CPAP, and CPAP further improves ISI

Rich et al, 2013; Wilkese et al 2013



Sweetman et al 2019

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Insomnia and YOU

Highly comorbid with other conditions-
92% have something else

May even be a "hand on the door" item, after you address what YOU thought the visit was about

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Gadermann et al 2012

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Consequences of Insomnia

Mental Health
- increased risk depression (1)
- Increased risk suicide (2)
- Trigger mood states (bipolar) (3)
- ADHD (4)

Social:
- reduced productivity, presenteeism (5)
- Impact on other treatments (reduced Compliance with CPAP (6))
- MVA (5)

Physical Health:
- cognitive deficits (7)
- HTN, CVD (8)
- NIDDM (9)
- Pain (10)
- All cause mortality (11)

1) Mai and Buysee 2008; Buysee et al 2008. 2) Pigeon, Pinquart and Connor 2012:meta-analysis; 3) Harvey et al 2009; Perlis et al 1997; 4)

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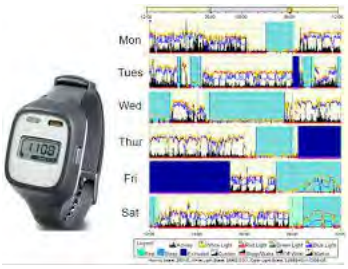
ASSESSMENT

HISTORY:
- onset, duration, management strategies tried
- Deep dive into schedule/ routines
- Next day impairment
- screen for other sleep disorders

TOOLS:
- Scales (ESS/ISI)
- Actigraph (sees hands-on session)
- Sleep diaries
- PSG- only if concerns for comorbidities



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INSOMNIA- ICSD3/DSM5

DSM-5 Definition of Insomnia Disorder

Dissatisfaction with sleep quality or quantity and ≥1 of the following:
- ❑ Difficulty initiating sleep
- ❑ Difficulty maintaining sleep
- ❑ Early morning wakening

Sleep disturbance occurs despite adequate opportunity for sleep

Sleep difficulty occurs ≥ 3 nights/wk for ≥ 3 months

APA. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. 2013.

*or taking a medication so as not to have such sx

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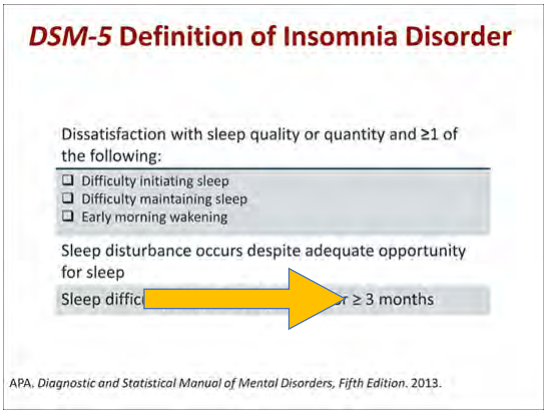
INSOMNIA- ICSD3/DSM5



*or taking a medication so as not to have such sx

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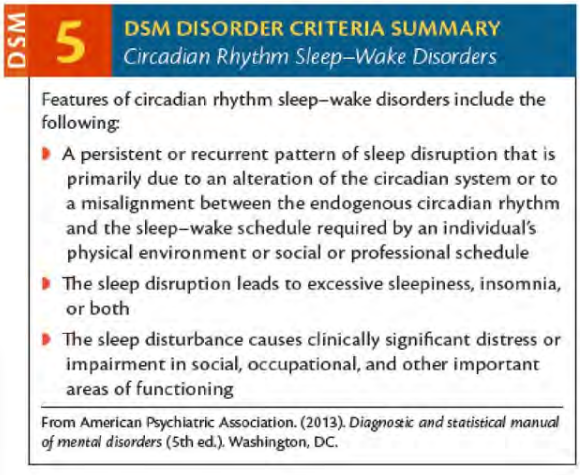
CIRCADIAN RHYTHM DISORDERS



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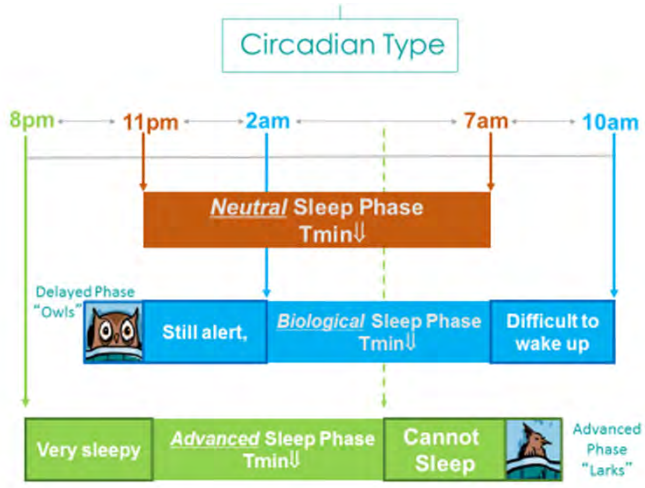
CIRCADIAN RHYTHM DISORDERS



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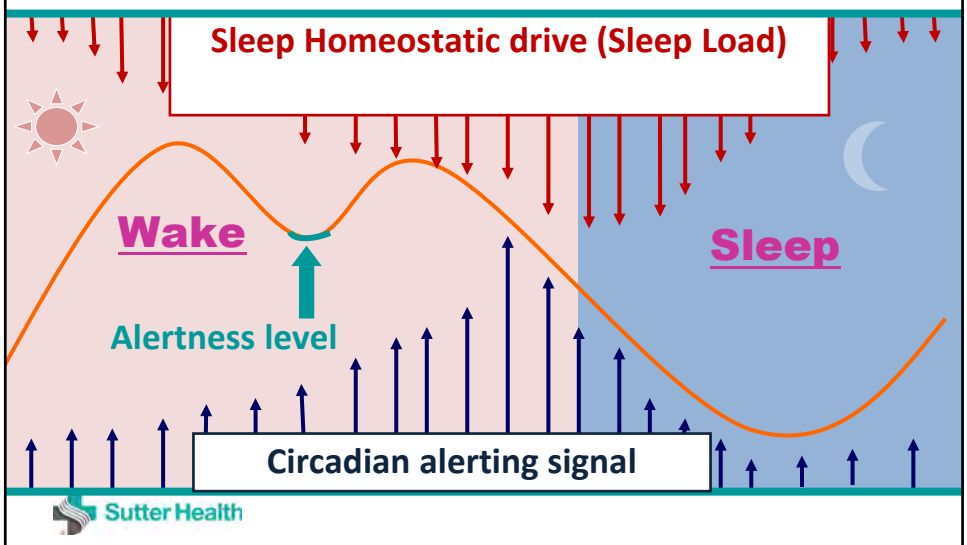
Interaction of Circadian Rhythms & Sleep



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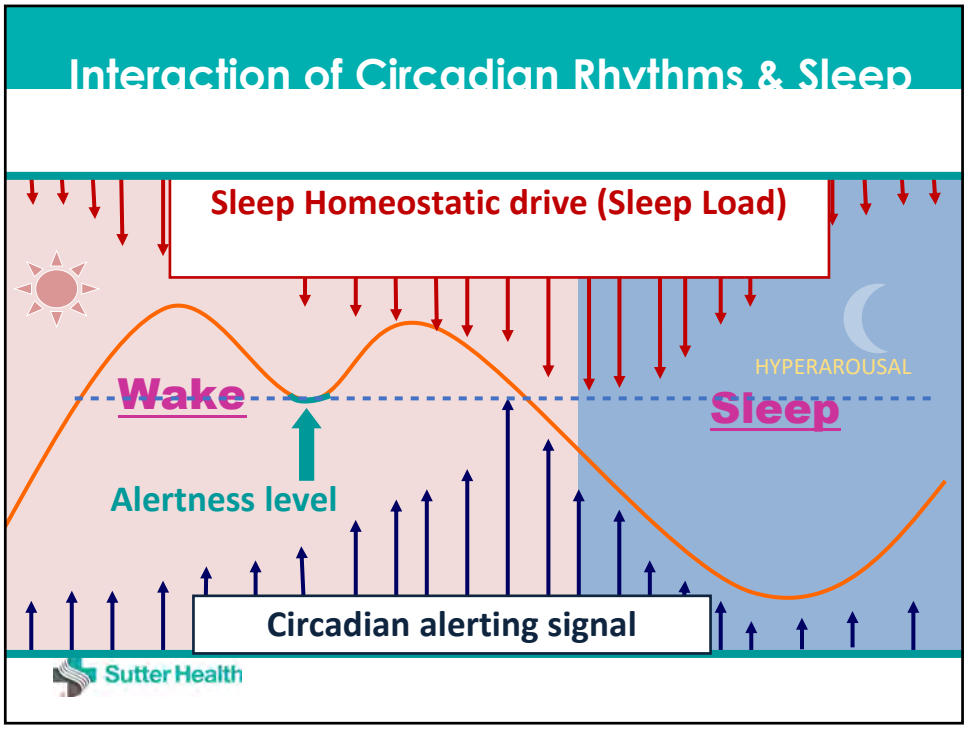
Interaction of Circadian Rhythms & Sleep
Sleep Homeostatic drive (Sleep Load)
HYPERAROUSAL
Wake
Sleep
Alertness level
Circadian alerting signal
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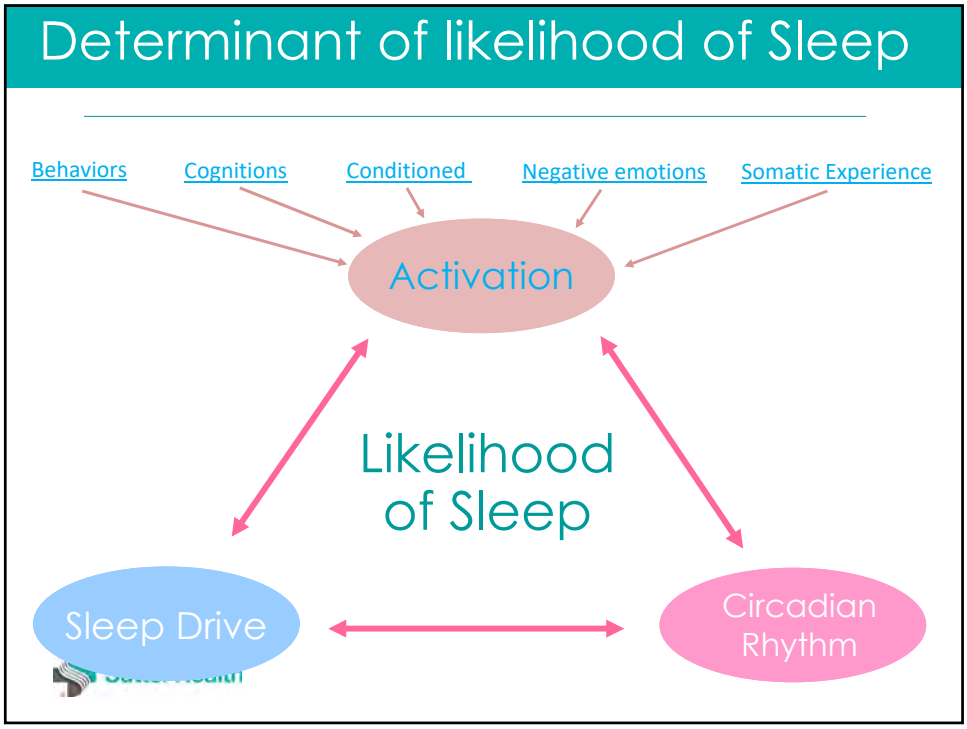
Determinant of likelihood of Sleep
Behaviors
Cognitions
Conditioned
Negative emotions
Somatic Experience
Activation
Likelihood of Sleep
Sleep Drive
Circadian Rhythm

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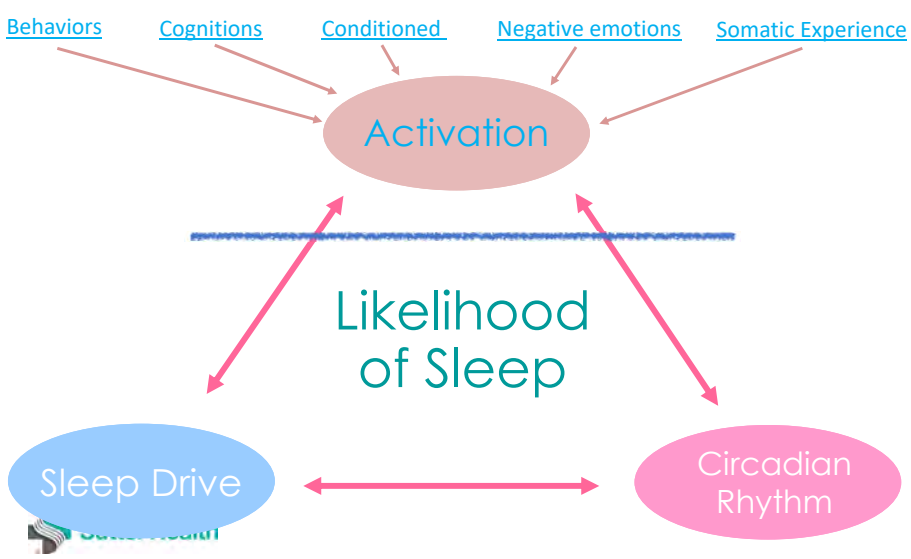
Determinant of likelihood of Sleep



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How Sleep Medications Work

- Activating Neurotransmitters:
  - Acetylcholine
  - Serotonin
  - Dopamine
  - Norepinephrine
  - Histamine
  - Orexin
- Inhibitory Neurotransmitters:
  - GABA
  - galanin

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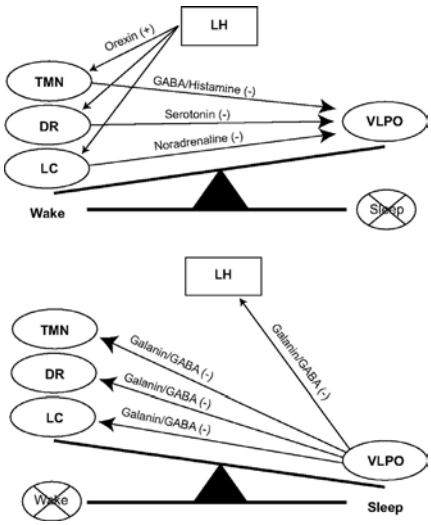
The "flip-flop" switch model of transitions between sleep and wakefulness



Ritchie E. Brown et al. Physiol Rev 2012;92:1087-1187

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Physiological Reviews

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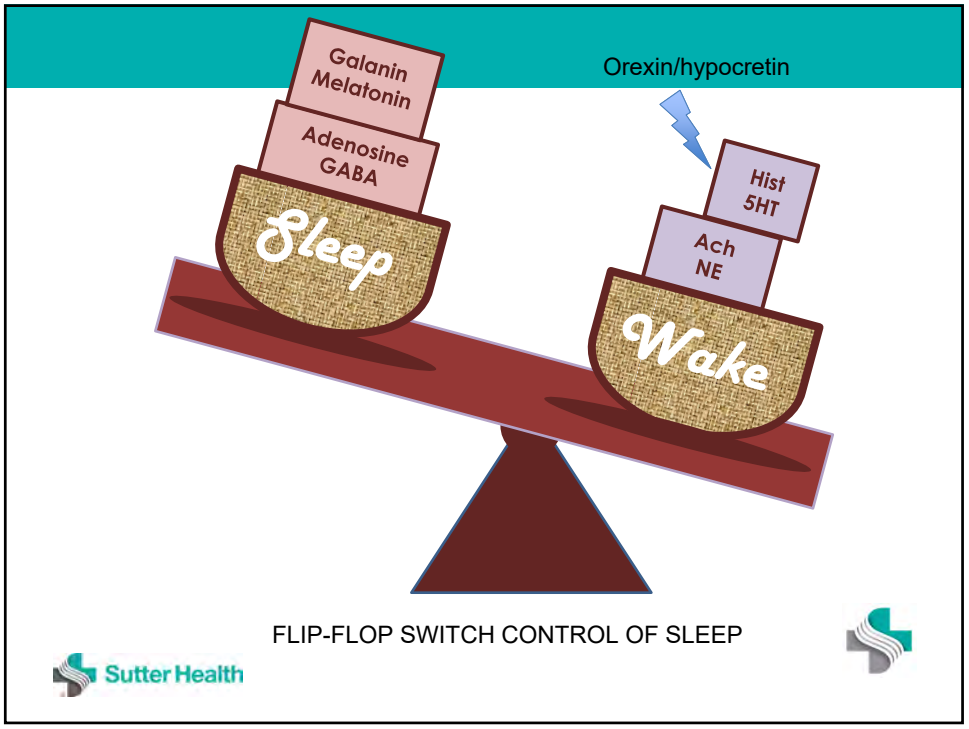

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AASM Treatment Guidelines

- 2008: “Psychological and behavioral interventions are effective and recommended in the treatment of chronic …insomnia.”
- 2021: “We recommend that clinicians use multicomponent cognitive behavioral therapy for insomnia for the treatment of chronic insomnia disorder in adults. (STRONG)”
- “….We suggest that clinicians not use sleep hygiene as a single-component therapy”

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Schutte-Rodin et al. 2008; Edinger et al 2021

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ACP American College of Physicians®
Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Management of Chronic Insomnia Disorder in Adults: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Devan Kansagara, MD, MCR; Mary Ann Forciea, MD; Molly Cooke, MD; and Thomas D. Denberg, MD, PhD; for the Clinical Guidelines Committee of the American College of Physicians*

Recommendation 1: *ACP recommends that all adult patients receive cognitive behavioral therapy for insomnia (CBT-I) as the initial treatment for chronic insomnia disorder. (Grade: strong recommendation, moderate-quality evidence)*

Recommendation 2: *ACP recommends that clinicians use a shared decision-making approach, including a discussion of the benefits, harms, and costs of short-term use of medications, to decide whether to add pharmacological therapy in adults with chronic insomnia disorder in whom cognitive behavioral therapy for insomnia (CBT-I) alone was unsuccessful. (Grade: weak recommendation, low-quality evidence)*

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Ann Inter Med, 2016

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MEDS- UPSHOT

SPECIAL ARTICLES

Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline

Michael J. Sateia, MD[1]; Daniel J. Buysse, MD[2]; Andrew D. Krystal, MD, MS[3]; David N. Neubauer, MD[4]; Jonathan L. Heald, MA[5]

[1]Geisel School of Medicine at Dartmouth, Hanover, NH; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA; [3]University of California, San Francisco, CA; [4]Johns Hopkins University School of Medicine, Baltimore, MD; [5]American Academy of Sleep Medicine, Darien, IL

*CBTI is standard of treatment, but consideration of treatment goal, comorbidities, treatment response, availability, safety, pt preference and cost

CBTI treatment failure: inability/unwillingness to apply recs, lack availability - or just non-responsive

Weak evidence for or against agents in all classes

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chart

Clinical Guidelines for Pharmacologic treatment of Insomnia

- All evidence rated WEAK
  - Prior meta-analyses show small/moderate effects sizes of benzos, benzoR agonists
    - Higher adverse effects
  - Glass et al 2005, NNT 13, NNH 6
  - Sedating antidepressants insufficient data

	Sleep Onset	Sleep Maintenance	
Suvorexant		+	
eszopiclone	+	+	
zaleplon	+		
zolpidem	+	+	
triazolam	+		
temazepam	+	+	
Ramelteon	+		
doxepin		+	
Trazodone	-	-	
Tiagabine	-	-	
diphenhydramine	-	-	
Melatonin	-	-	
tryptophan	-	-	
valerian	-	-	

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Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice guideline for the pharmacologic treatment of chronic insomnia in adults:an AASM Clinical practice guideline. JCSM. 2017;13(2):307-349.

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Clinical Guidelines for Pharmacologic treatment of Insomnia

- All evidence rated WEAK
  - Prior meta-analyses show small/moderate effects sizes of benzos, benzoR agonists
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	Sleep Onset	Sleep Maintenance
Suvorexant		+
eszopiclone	+	+
zaleplon	+	
zolpidem	+	+
triazolam	+	
temazepam	+	+
Ramelteon	+	
doxepin		+
Trazodone	-	-
Tiagabine	-	-
diphenhydramine	-	-
Melatonin	-	-
tryptophan	-	-
valerian	-	-

Versus nothing!

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Clinical Guidelines for Pharmacologic treatment of Insomnia

- All evidence rated WEAK
  - Prior meta-analyses show small/moderate effects sizes of benzos, benzoR agonists
    - Higher adverse effects
  - Glass et al 2005, NNT 13, NNH 6
  - Sedating antidepressants insufficient data

	Sleep Onset	Sleep Maintenance	Benefits:Harms
Suvorexant		+	B>H
eszopiclone	+	+	B>H
zaleplon	+		B>H
zolpidem	+	+	B>H
triazolam	+		B=H
temazepam	+	+	B>H
Ramelteon	+		B>H
doxepin		+	B>H
Trazodone	-	-	B<H
Tiagabine	-	-	B<H
diphenhydramine	-	-	B=H
Melatonin	-	-	B=H
tryptophan	-	-	B<H
valerian	-	-	B=H

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COMPARISON MED CLASSES EFFECT ON SLEEP, V CBTI

V. Placebo	SL: PSG (min)	SL: Sleep Diary (min)	WASO: PSG (min)	WASO: Sleep Diary (min)	SE%: PSG	SE%: sleep diary	TST: PSG	TST: Sleep diary	Risk Difference (from placebo)
Benzodiazepine	-10	-19.6	-16.7	-39.9	7.4%	7.9%	32.7	52.6	0.15
Non-benzodiazepine	-12.8	-17	-7.0	-15.0	4.7%	5.0%	11.4	31.5	0.07
Antidepressant	-7.0	-12.2	-12.2	-7.1	13.6%	N/A	79.6	-54.3	0.09
CBT-I		-19.03		-26		9.91%			—
DORA	-10.15	-9.37	-24.11	-9.13	7.61%	5.84%	30.75	19.16	RR: 1.06

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Bucemi et al. 2007, Huedo-Medina 2012; Trauer et al 2015; Xue et al 2021

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Pharmacologic properties

Table 1
Basic pharmacology of medications used to treat insomnia

Agent	Trade name	Class	FDA indication	t_{max} (h)	$t_{1/2}$ (h)	Binding profile							Metabolism
						Benzo binding	Anti-H1	MT1–MT2	Anti-5HT2	Anti-alpha-1	Anti-dopa	Anti-mAch	
Flurazepam	Dalmane	Benzodiazepine	Insomnia	0.5–1.5	40–250	+++							CYP2C19, CYP3A4
Quazepam	Doral	Benzodiazepine	Insomnia	2	20–120	+++							CYP3A4, CYP2C19
Estazolam	Prosom	Benzodiazepine	Insomnia	1.5–2	10–24	+++							CYP3A4
Temazepam	Restoril	Benzodiazepine	Insomnia	1–3	8–20	+++							Glucuronide conjugation
Triazolam	Halcion	Benzodiazepine	Insomnia	1–3	2–5.5	+++							CYP3A4, glucuronide conjugation
Clonazepam	Klonopin	Benzodiazepine	Seizures, anxiety	1–2	35–40	+++							CYP2B, CYP3A4, acetylation
Lorazepam	Ativan	Benzodiazepine	Anxiety	1–3	12–15	+++							Glucuronide conjugation
Alprazolam	Xanax	Benzodiazepine	Anxiety	1–3	12–14	+++							CYP3A4/5, CYP2C19
Diazepam	Valium	Benzodiazepine	Anxiety, muscle spasm, seizures	0.5–2	20–50	+++							CYP2B, CYP2C19, CYP3A4, glucuronide conjugation
Chlordiazepoxide	Librium	Benzodiazepine	Anxiety, ETOH withdrawal	0.5–4	5–100	+++							CYP2B, CYP2C19, CYP3A4, glucuronide conjugation
Zolpidem (MR)	Ambien	Imidazopyridine	Insomnia	1.7–2.5	2.0–5.5	+++							CYP3A4, CYP1A2, CYP2C9
Zaleplon	Sonata	Pyrazolopyrimidine	Insomnia	1.1	0.9–1.1	+++							Aldehyde oxidase, CYP3A4
Eszopiclone	Lunesta	Cyclopyrrolone	Insomnia	1.3–1.6	6–7	+++							CYP3A1, CYP2E1
Ramelteon	Rozerem	Propionamide	Insomnia	0.7–0.95	0.8–2			+++					CYP1A2, CYP2C, CYP3A4
Amitriptyline	Elavil	Tertiary amine tricyclic	MDD	2–5	10–100		+++			+++		+++	CYP3A4, CYP2C19, CYP2D6, CYP2C9
Doxepin	Sinequan	Tertiary amine ricyclic	MDD, anxiety	1.5–4	10–50		+++			+++		+	CYP3A4, CYP2C19, CYP2D6, CYP2C9, CYP1A2
Trazodone	Desyrel	Chlorophenylpiperazine	MDD	1–2	7–15				+++	+++			CYP3A4, CYP2D6, CYP1A2
Mirtazapine	Remeron	Tetracyclic	MDD	0.25–2	20–40		+++		+++				CYP2D6, CYP1A2, CYP3A4
Quetiapine	Seroquel	Dibenzothiazepine derivative	Schizophrenia mania	1	7		++		+	+++	+		CYP2D6, CYP3A4
Olanzapine	Zyprexa	Thiobenzodiazepine	Schizophrenia mania	5	30		+++		+++	++	++	+++	CYP1A2
Risperidone	Risperdal	Benzisoxazole derivative	Schizophrenia mania	1	3–20		+		+++	+++	++		CYP2D6, CYP3A4
Diphenhydramine	Benadryl	Ethanolamine	Allergy, OTC sleep aid	2–3	5–11		+++					+++	CYP2D6, CYP1A2, CYP2C9, CYP2C19
Doxylamine succinate	Unisom	Ethanolamine	Allergy, OTC sleep aid	1.5–2.5	10–12		+++					+++	CYP2D6, CYP1A2, CYP2C9

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Krystal 2009

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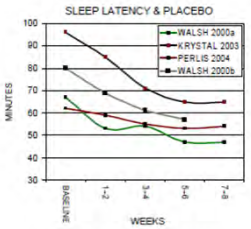
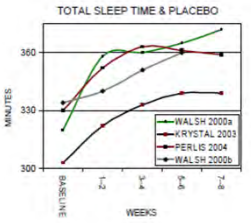
POWER OF PLACEBO

- Meta-analysis of placebo effect (2003)
  - Subjective SL: -13.1 +/- 2 min
  - Subjective TST: 13.5 +/- 5.4 min
  - PSG: - 2.5min (non sig)
  - ~20% change attributable to placebo
- Cause?
  - Regression to mean
  - Hawthorne effect
  - Expectancy (belief will improve)*
  - Cognitive dissonance ("of course I'm getting better, not wasting my time with this")
  - Effect of pill itself (reduced worry)





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McCall, Augustino, Dunn meta-anlysis 2003; Perlis et al review 2005

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2015 META- ANALYSIS

- Small to large effect sizes for placebo:
  - sleep onset
  - TST
  - WASO
  - SE

Table 2—Pooled Within-Group Effect Sizes for Drug Treatment and Proportion of Placebo Response to Drug Response.

Outcome	k	g	95% CI	P	Placebo response (%)
Objective outcomes					
SOL	41	−0.55**	−0.63, −0.46	< 0.001	64
TST	38	0.79**	0.69, 0.88	< 0.001	53
WASO	35	−0.55**	−0.66, −0.44	< 0.001	53
SE	41	0.64**	0.55, 0.73	< 0.001	48
Subjective outcomes					
sSOL	22	−0.45**	−0.57, −0.34	< 0.001	64
sTST	25	0.54**	0.42, 0.65	< 0.001	80
sWASO	11	−0.29**	−0.42, −0.16	< 0.001	100
sSE	5	0.64**	0.39, 0.89	< 0.001	39
sQuality	22	0.51**	0.37, 0.65	< 0.001	61

*P < 0.05, **P < 0.01. CI, confidence interval; k, number of treatment conditions in the analysis; Placebo Response, proportion of placebo effect to pre-post pharmacological effect in percent; SE, sleep efficiency; SOL, sleep onset latency; sSE, subjective sleep efficiency; sQuality, subjective quality; sSOL, subjective sleep onset latency; sTST, subjective total sleep time; sWASO, subjective wake after sleep onset; Sub., subjective; TST, total sleep time; WASO, wake after sleep onset.

Table 2 shows that subtracting the mean placebo response rates from mean drug response rates revealed that 39% (sSE) to 100% (sWASO) of the response to the medications under investigation are reported in the placebo group as well. In fact, one outcome variable (sWASO) placebo treatment was even more effective than the pharmacological therapy. The pooled proportion of the placebo response to the drug response was 63.56% (SD = 20.92).

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Winkler A, Rief W. Effect of placebo conditions on polysomnographic parameters in primary insomnia: a meta-analysis. *SLEEP* 2015;38(6):925–931.

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Key suggestion for changing practice

Don't start a medication without thorough evaluation of behaviors

- will just be frustrating for both of you!

Don't jump from one to another or add without examining why failing

Don't start without thinking of exit strategy

Avoid prns to reduce reliance

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OPEN TO TRY CBT-I?

Refer out?

Vet your providers well

CBTI is NOT:

Sleep hygiene

Relaxation tools

APCs?

Great option, if you have those that are willing to train

Online certification

PESI

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OPEN TO TRY CBT-I?

Online?
- Evidence based:
- Somryst- FDA authorized, requires Rx
- Sleepio- may be free!

Others exist, but do not necessarily have efficacy data published
- mysleepfitness.com
- VA: Path to Better Sleep

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META-ANALYSIS ICBT-I

V. Placebo	SL: PSG (min)	SL: Sleep Diary (min)	WASO: PSG (min)	WASO: Sleep Diary (min)	SE%: PSG	SE%: sleep diary	TST: PSG	TST: Sleep diary
Ye et al. 2016		-18.41		-22.3		9.58%		22.3
Seyffert et al 2016		-11		-20		7.22%		20

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OPEN TO TRY CBT-I?

ONLINE CONTRAINDICATIONS:

Unknown/ suspected OSA not currently treated

Excessive daytime sleepiness

Conditions or lifestyle situations in which sleep restriction or excessive sleepiness could cause risk (parasomnias, seizure disorder, bipolar, operating heavy machinery)

Relative contraindications:

Use of sleep aids/ medications with intent to taper

High anxiety

Limited motivation/ self efficacy

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Case Report 1:

- MB is a 44-year-old male who works in marketing, who reports sleep problems for 15-20 years. Previously, he would wake up and when difficulty sleeping, start working. However, since SIP and having to also care for his young toddler, his sleep patterns became unsustainable. He had been escalating use of OTC sleep aids prior to evaluation.

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Case Report 1:

- Over 6 weeks, his sleep efficiency (SE%, how much of the time spent trying to sleep, was actually sleeping) improved:

No sleep aids!

  - Week 1: 57.05%
  - Week 6: 92.4%

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Case Report 2:

- JK is a 66-year-old woman who runs her own business, and frequently travels to the East Coast for work. She developed insomnia after menopause, and had been using sleep aids, but they caused next day sedation. She was also using her Oura ring, and felt like she was trying everything, and was really frustrated with her sleep.

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- JK was continued on her previously prescribed CPAP and

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Case Report 2:

- Over the course of CBTI, her SE% remained stable, her ISI reduced from 15 —> 6 and she reduced use of sleep aid to only with travel

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- Two months later, reported that

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Case Report 3:

- LH is a 32-year-old woman working for a large tech company and finishing school, who felt increased stress and sleep disruption with COVID shelter in place restrictions

- LH was referred to an online CBTI program

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Case Report 3:

- Over the course of 6 weeks:
  - SE% improved from 74% to 91%
  - Her ISI reduced from 17-7

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Summary

Insomnia is highly prevalent, and impacts all areas of medicine

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Summary

- Insomnia is highly prevalent, and impacts all areas of medicine
- Ability to sleep is controlled by
  - the two process model
  - flip- flop switch

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Summary

- Insomnia is highly prevalent, and impacts all areas of medicine
- Ability to sleep is controlled by
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- CBTI is recommended- first line

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Summary

- Insomnia is highly prevalent, and impacts all areas of medicine
- Ability to sleep is controlled by
  - the two process model
  - flip- flop switch
- CBTI is recommended- first line
- medications, if recommended, will work better with behavioral modification as well

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Thank you!

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Restless Legs Syndrome Management

11:35 a.m. – 12:20 p.m.

RAFAEL ZUZUARREGUI, MD
SAN FRANCISCO HEALTH CARE SYSTEM
UC SAN FRANCISCO

Dr. Rafael Zuzuárregui is Director of the San Francisco PADRECC and Assistant Professor of Neurology at University of California San Francisco (UCSF). He is board certified in Neurology and fellowship-trained in Movement Disorders and Sleep Disorders. Dr. Zuzuarregui earned his medical degree, completed his residency in Neurology, served as Chief Resident, and completed his Movement Disorders Fellowship at Boston University School of Medicine. He also completed his Sleep Disorder Fellowship at Stanford University School of Medicine. Dr. Zuzuárregui's clinical focus is in the treatment of Movement Disorders and various sleep disorders, as well as the use of Botox and Deep Brain Stimulation (DBS). His research is on the intersection between movement and sleep disorders with particular focus with the impact of DBS on various sleep parameters.

Restless Legs Syndrome Management

Rafael Zuzuarregui, MD
Assistant Clinical Professor, UCSF Movement Disorders and Neuromodulation
Director, PADRECC, San Francisco VAMC

1

Disclosures

- No disclosures

2

Learning Objectives

- Recognize symptoms of restless legs syndrome (RLS)
- Identify first line agents for treatment of RLS
- Understand side effect profiles of medications used for the treatment of RLS
- Identify augmentation and impulse control disorders

3

Presentation Outline

- Epidemiology
- Clinical features
- Pathophysiology
- Diagnosis
- Management

4

RLS - Epidemiology

- Prevalence is 4% to 29% in the general North American population
- F>M
  - This difference disappears when only nulliparous women are evaluated
- Genetic component
  - 40-60% of patients have a family member with RLS
  - Not tied to one gene, but multiple loci

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Presentation Outline

- Epidemiology
- Clinical features
- Pathophysiology
- Diagnosis
- Management

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RLS – Clinical Features

- Restless Legs Syndrome (RLS)
  - 1) urge to move one's extremities, often due to severe discomfort
  - 2) arises during periods of rest
  - 3) worse at night
  - 4) usually relieved by movement
  - 5) not attributable to another disorder
    - 80% of RLS cases have Periodic Limb Movement Disorder (PLMD), which occurs during sleep
    - These are separate clinical entities

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RLS – Clinical Features

Table 2
Descriptive terms for restless legs syndrome

Creepy-crawly
Ants crawling
Jittery
Pulling
Worms moving
Soda bubbling in the veins
Electric current
Shock-like feelings
Pain
The gotta moves
Burning
Jimmy legs
Heebie jeebies
Tearing
Throbbing
Tight feeling
Grabbing sensation
Elvis legs
Itching bones
Crazy legs
Fidgets

8

RLS – Clinical Features

- Risk factors
  - Systemic iron deficiency
  - Renal failure
  - Pregnancy
  - Multiple sclerosis
  - Neuropathy
  - PD?

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RLS – Clinical Features

- Symptoms may be worsened by such medications as:
  - Selective serotonin reuptake inhibitors (SSRIs) or mixed serotonergic antidepressants
  - Tricyclic antidepressants
  - Antihistamines
  - Dopamine antagonists
- Wellbutrin is the only antidepressant that does not affect RLS

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Presentation outline

- Epidemiology
- Clinical features
- Pathophysiology
- Diagnosis
- Management

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RLS - Pathophysiology

- Dopamine deficiency?
  - ?Increased prevalence of RLS in Parkinson's disease
  - Studies have shown an increase in DA metabolite 3-ortho-methyldopa (3-OMD) in CSF of RLS patients compared to controls
  - 3- OMD levels are increased during the day but reduced at night
    - Diurnal pattern of DA activity
  - An unclear mechanism thus far

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RLS - Pathophysiology

- Relative dopamine excess
  - Hyperdopaminergic state leads to a downregulation of DA receptors
    - Diurnal dopamine secretion
  - If ↓ in DA activity at night and ↓ in overall DA receptors may explain RLS symptoms

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RLS - Pathophysiology

- Brain iron deficiency
  - Multiple studies have shown a deficiency in CSF>serum ferritin levels
  - Animals with iron deficiency have:
    - Increases of tyrosine hydrolaze in the basal ganglia
      - Leads to increased extracellular DA levels
    - Reduction in caudate and putamen DA receptors also seen
  - Generalized downregulation of adenosine A_1 receptors
  - Hypersensitivity of corticostriatal glutamatergic terminals

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Presentation Outline

- Epidemiology
- Clinical features
- Pathophysiology
- Diagnosis
- Management

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RLS - Diagnosis

- Strictly a clinical diagnosis made based on consensus criteria
  - 1) urge to move one's extremities, often due to severe discomfort
  - 2) arises during periods of rest
  - 3) worse at night
  - 4) usually relieved by movement
  - 5) not attributable to another disorder

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RLS - Diagnosis

- Mimickers of RLS include:
  - Nocturnal leg cramps
  - Peripheral neuropathy
  - Akathisia
  - Lumbar radiculopathy
  - Peripheral arterial claudication

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RLS - Diagnosis

- Polysomnography (PSG) cannot diagnosis RLS
  - Only PLMs can be seen on PSG
- For new onset RLS, serum ferritin levels and transferrin saturation index should be measured

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Presentation Outline

- Epidemiology
- Clinical features
- Pathophysiology
- Diagnosis
- Management

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RLS Management

- Non-pharmacologic measures
  - Remove offending agents
  - Avoidance of alcohol or caffeine
  - Involvement in regular mild to moderate exercise
  - Devices for treatment of RLS are limited
    - Hands-on session

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RLS - Management

- Iron supplementation
  - Ferritin levels <75 ng/ml and/or transferrin saturation index <45% should warrant supplementation

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RLS - Management

- Iron supplementation
  - RCT evaluated oral iron supplementation for RLS over 12 weeks (n=18)
    - Ferrous sulfate 325mg twice daily with Vitamin C 100mg
    - IRLS scores for iron (24.8 ± 5.72) and placebo (23.0 ± 5.03) improved
    - IRLS score reduction in iron (10.3 ± 7.40) v. placebo (1.14 ± 5.64) was significant (p = 0.01)

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RLS - Management

- Iron supplementation
  - Ferric carboxymaltose
    - Multiple studies evaluated patients OFF meds
    - Largest RCT evaluated 110 patients to FCM 1000mg v. placebo
      - Serum ferritin <75 µg/l OR transferrin saturation <20% and serum ferritin <300 µg/l
    - Baseline IRLS score 25.9 +/- 5.65 (iron) v. 26.0 +/- 5.78 (placebo)

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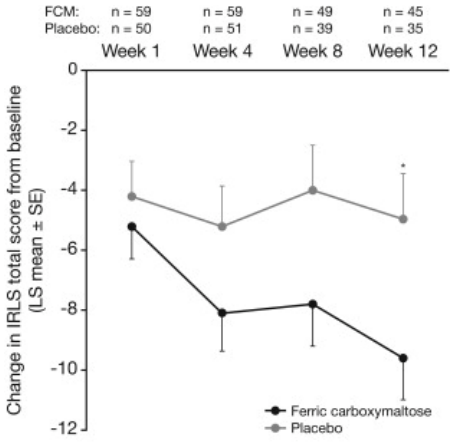
RLS - Management



*P = 0.021
FCM, ferric carboxymaltose; IRLS, International Restless Legs Scale; LS, least squares; SE, standard error.

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RLS - Management

- Iron supplementation
  - Ferric carboxymaltose
    - Most recent RCT focused on RLS in iron deficiency anemia
    - 29 patients with serum hemoglobin <12 g/dL AND either ferritin <20 ng/ml OR ferritin <100 ng/ml with transferrin saturation <18%
    - 1000mg initially, then 500mg a week later

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RLS - Management

		FCM (n = 15)	Placebo (n = 14)	p
IRLS	Week 6	12.13 ± 8.57	26.57 ± 5.43	0.000
	Week 6-Baseline	−13.47 ± 7.38	1.36 ± 3.59	0.000
VAS	Week 6	27.86 ± 27.51	56.07 ± 29.23	0.014[a]
	Week 6-Baseline	−41.07 ± 28.57	−9.29 ± 21.65	0.003
RLS Qol	Week 6	71.83 ± 28.29	63.04 ± 14.19	0.297
	Week 6-Baseline	4.83 ± 22.79	−1.96 ± 9.16	0.300
ISI	Week 6	8.79 ± 6.17	13.36 ± 5.02	0.041
	Week 6-Baseline	−6.00 ± 5.20	−0.36 ± 6.42	0.017
PSQI	Week 6	7.07 ± 3.71	12.00 ± 3.01	0.001
	Week 6-Baseline	−5.40 ± 3.72	0.43 ± 3.80	0.000

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RLS - Management

- Recommendations for treatment
  - Primary therapy
    - Oral for intermittent/mild symptoms with serum ferritin <75µg/l
    - IV therapy for moderate to severe symptoms with serum ferritin <300 µg/l or transferrin saturation <45%
  - Oral: Ferrous sulfate 325mg (elemental iron 65mg) daily or every other day with vitamin C 100mg
  - IV: Ferrous carboxymaltose 1000mg
  - Duration of therapy guided by labwork

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RLS - Management

- Historical first line agents
  - Dopamine agonists
    - Pramipexole
    - Ropinirole
    - Rotigotine
- Recommended first line agents
  - Alpha-2-delta ligands
    - Pregabalin
    - Gabapentin Enacarbil
    - Gabapentin
- If augmentation or failure on multiple first/second line agents
  - Opiates

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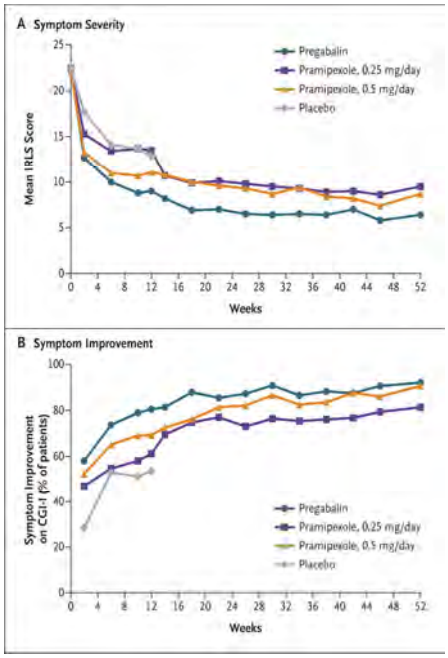
RLS - Management

- Recommended first line agents
  - Alpha-2-delta ligands
    - Pregabalin
    - Gabapentin Enacarbil
    - Gabapentin
- Second line agents
  - Dopamine agonists
    - Pramipexole
    - Ropinirole
    - Rotigotine
  - Dipyridamole
- If augmentation or failure on multiple first/second line agents
  - Opiates

29

Pregabalin

- Evidence based on large RCT v. pramipexole
  - Evaluated RLS severity scores after 12 weeks
    - Pregabalin 300mg: 22.3 ± 5.7 to 10.9 ± 7.3
    - Pramipexole 0.25mg: 22.4 ± 5.4 to 14.6 ± 7.3
    - Pramipexole 0.5mg: 22.1 ± 5.2 to 12.0 ± 7.5
  - Similar differences maintained at 52 weeks



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Pregabalin

- No significant differences between the higher dose of pramipexole and pregabalin
- Less augmentation was seen with pregabalin in this study at 52 weeks
  - Pregabalin 1.7%; pramipexole 0.25mg 6.6%; pramipexole 0.5mg 9.0%

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Pregabalin

- Recommendations for treatment
  - Primary therapy
  - Starting dose 25-50mg up to total 450mg daily
    - Often will use bid or tid dosing for augmentation

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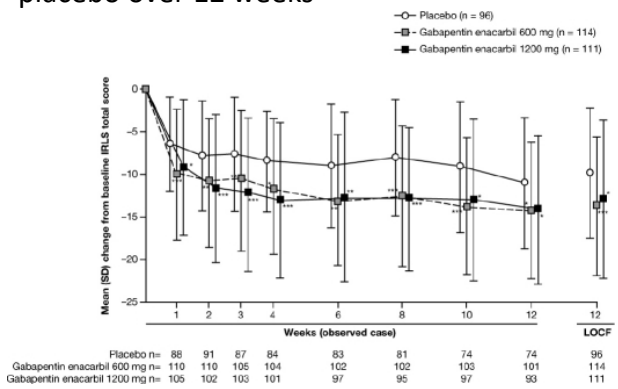
Gabapentin Enacarbil

- Long-acting form of Gabapentin evaluated by multiple double-blind RCTs
  - One RCT (n=325) evaluated GEn 1200mg v. GEn 600mg v. placebo over 12 weeks



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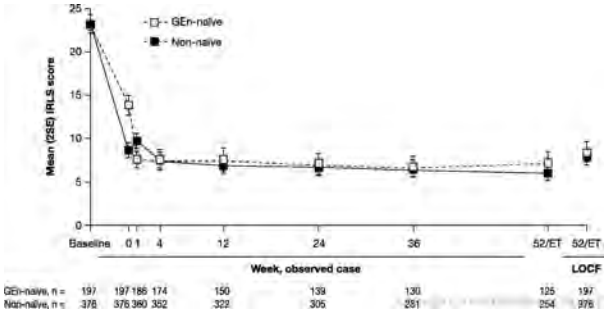
Gabapentin Enacarbil

- One study evaluated participants from four of the original 12 week trials (n=573)
  - 1200mg daily at 5pm with ability to adjust dose to 600mg/1800mg over 52 weeks



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Gabapentin Enacarbil

- Recommendations for treatment
  - Primary therapy
  - Dose range 300-600mg taken with dinner

35

Gabapentin

- Considered efficacious for RLS symptoms
  - Use of gabapentin in RLS is based on early case series with limited number of patients in each study
- Ease of access, tolerability and low interaction with other meds make it an attractive option

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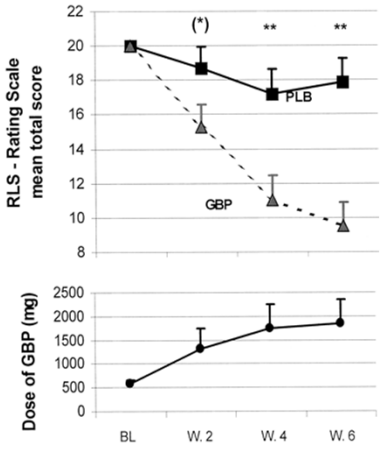
Gabapentin

- One crossover RCT (n=22) evaluated gabapentin v. placebo over 6 weeks with 1 week washout
  - 600mg titrated up to max 2400mg daily spread over two doses
  - Significant reduction in gabapentin group (20 to 9.5±1.35) compared to placebo (20 to 17.9±1.35)



37

Gabapentin

- Recommendations for treatment
  - Primary therapy
  - Dose range 300-1500mg qhs
    - Renally excreted, so dose may need to be adjusted
    - Often will use bid or tid dosing for augmentation

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Pramipexole

- Double-blind RCT (n=190) with 0.25mg, 0.5mg or 0.75mg dose v. placebo
  - At 12 weeks, pramipexole significantly reduced the mean RLS severity by a difference of 3.8 points more than placebo
    - -13.2 ± 0.7 vs -9.4 ± 0.6; p <0.01
  - Majority of patients on 0.5mg

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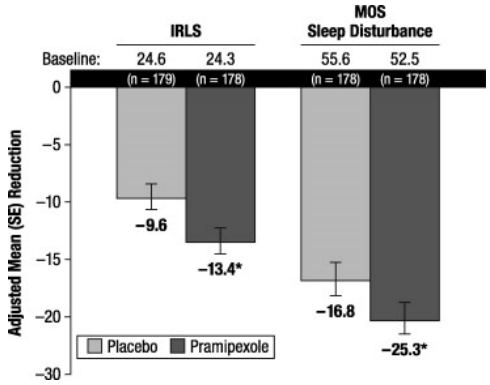
Pramipexole

- An earlier study (n=369) of 0.25mg, 0.5mg or 0.75mg dose v. placebo demonstrated the same difference in RLS scores after 12 weeks
  - Most subjects on 0.25mg or 0.5mg



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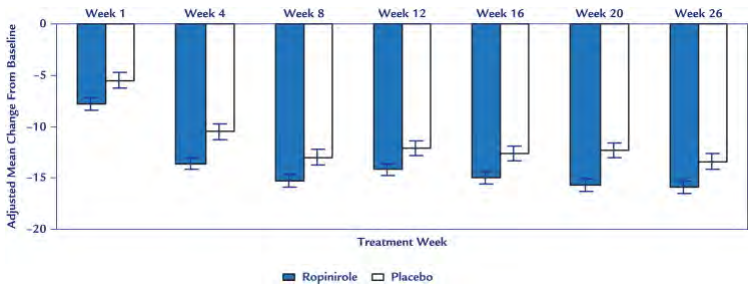
Pramipexole

- Recommendations for treatment
  - Adjunctive therapy
  - Dose range 0.125mg-0.5mg qhs
    - Higher doses increase the risk of augmentation/ICDs

41

Ropinirole

- Double-blind RCT (n=296) in moderate RLS (RLS ≥24) used 0.25mg-4mg v. placebo
  - Median dose of 1.8mg (range 0.3-3.6mg) was used
  - Both groups with improvements in total IRLS scores
    - Ropinirole group had a lower IRLS score of 2.1 points than placebo at 26 weeks ($p<0.05$)



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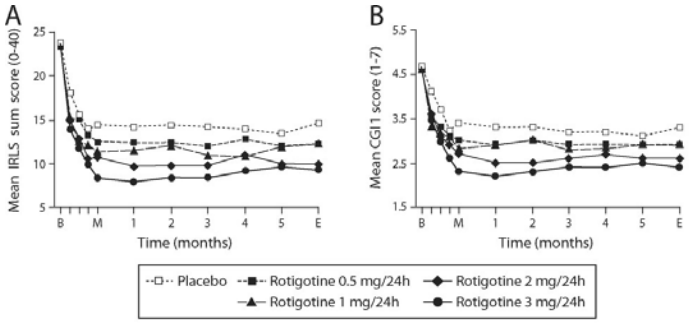
Ropinirole

- Recommendations for treatment
  - Adjunctive therapy
  - Dose range 0.5mg-2mg qhs
    - Higher doses increase the risk of augmentation/ICDs

43

Rotigotine

- Double-blind RCT (n=285) multiple doses v. placebo
  - At 6 months, IRLS scores significantly lower than placebo for 2mg and 3mg (-4.5 and -5.2 respectively; p<0.001)
  - Patients with severe insomnia at baseline showed biggest improvement in RLS scores



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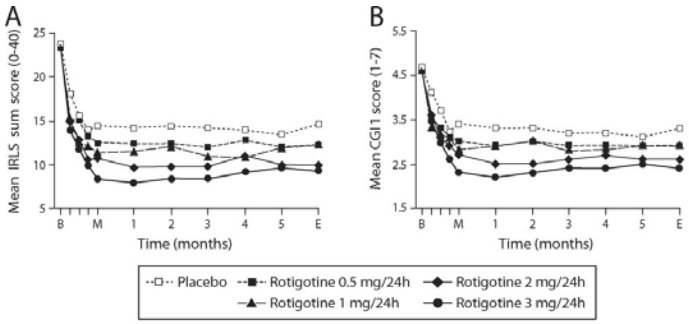
Rotigotine

- ?augmentation on higher doses
- Placebo effect



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Rotigotine

- Recommendations for treatment
  - Adjunctive therapy
  - Dose range 1-2mg daily

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Levodopa

- Evidence supporting its use mostly based on case series and randomized controlled trials that did not employ RLS severity scales
- A recent meta-analysis demonstrated a significant improvement of RLS severity compared to placebo using CGI-I ($p<0.0001$)

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Levodopa

- Recommendations for treatment
  - Adjunctive therapy
  - One-half to full tab of Sinemet IR 25-100 or Sinemet CR 50-200
    - Much higher risk of augmentation compared to pramipexole or ropinirole
    - Restrict use to PD population

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Dopamine Agents - Augmentation

- Direct effect of dopaminergic therapy
  - Paradoxical response
  - Worsening of symptom severity at least 5 of 7 days per week
  - Symptoms occur earlier in the day and can spread to previously unaffected body parts
  - Leads to increases in dopaminergic medication or addition of other agents
  - Levodopa may cause augmentation at a rate of 30% of patients, while pramipexole and ropinirole are at 10%

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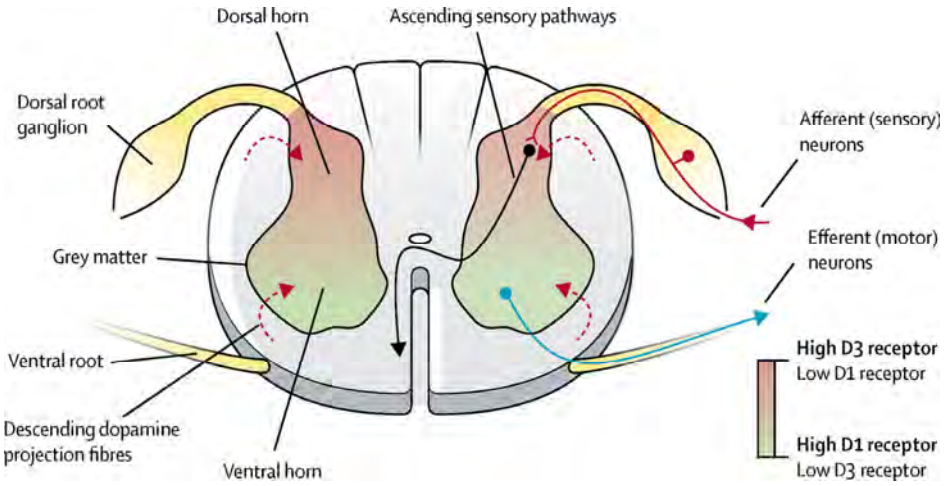
Dopamine Agents - Augmentation

- Dopaminergic agents that target the inhibitory D3 receptor are initially effective
  - Reduces afferent sensory signals
- However, long-term use of dopaminergic agonists results in upregulation of the excitatory D1 receptor
  - Increases efferent motor signals

50

Dopamine Agents - Augmentation



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Dopamine Agents - ICDs

- Patients with augmentation appear to have a six-times higher risk of developing impulse control disorders (ICDs)
  - Pathologic gambling, shopping, spending money
  - Sexual behaviors
  - Eating
- Elevated risk likely related to use of dopamine medications, but may also represent an underlying tendency of RLS patients to develop ICDs

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Dopamine Agents

- Strategies to avoid augmentation and/or ICDs include utilizing long-acting dopamine agonists or shifting to other first-line agents for RLS
- Use of other first line agents significantly reduces the risk of these side effects
  - 2-3% risk with pregabalin in RCT v. pramipexole

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Dipyridamole

- Inhibits adenosine uptake by cells
  - Increases extracellular adenosine levels
- Recent RCT compared dipyridamole to placebo over two weeks
  - Dose up to 300mg (mean dose ~217mg)
  - Dipyridamole: IRLS 24.1 ± 3.1 to 11.1 ± 2.3
  - Placebo: IRLS 23.7 ± 3.4 to 18.7 ± 3.2 ($P < 0.001$)

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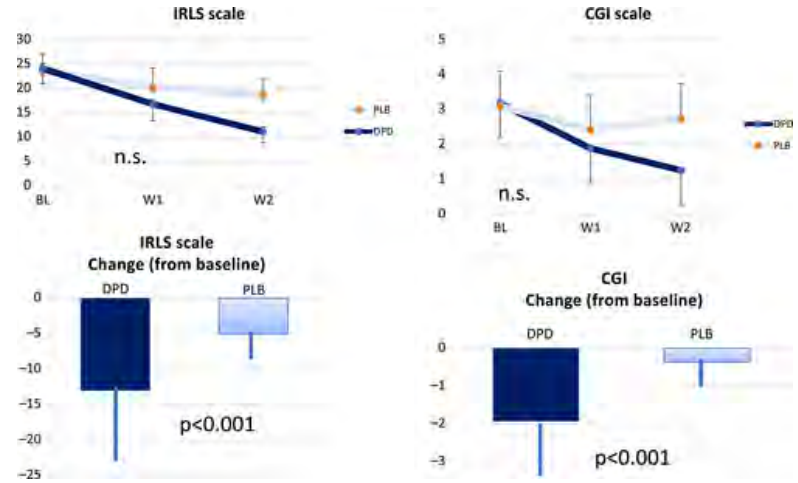
Dipyridamole



SE: Headache, abdominal distension, dizziness, bleeding

55

Dipyridamole

- Recommendations for treatment
  - Adjunctive therapy
  - Max dose 200mg bid
    - Often limited by side effect
    - 100mg bid has clinically been helpful

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Opiates

- RCT evaluated prolonged release oxycodone/naloxone v. placebo (n=306) over 12 weeks with 40 week open-label extension
  - Subjects with RLS for mean 10.3 ± 10 years and received RLS treatment for mean 5.0 ± 4.2 years
  - Mean daily dose for oxycodone 21·9 mg (15·0), naloxone 11·0 mg (7·5) and 34·4 mg (19·4) for placebo
  - Ten of 150 (7%) patients in oxycodone–naloxone group versus 46 of 154 (30%) in placebo group received the highest daily dose of 80 mg daily

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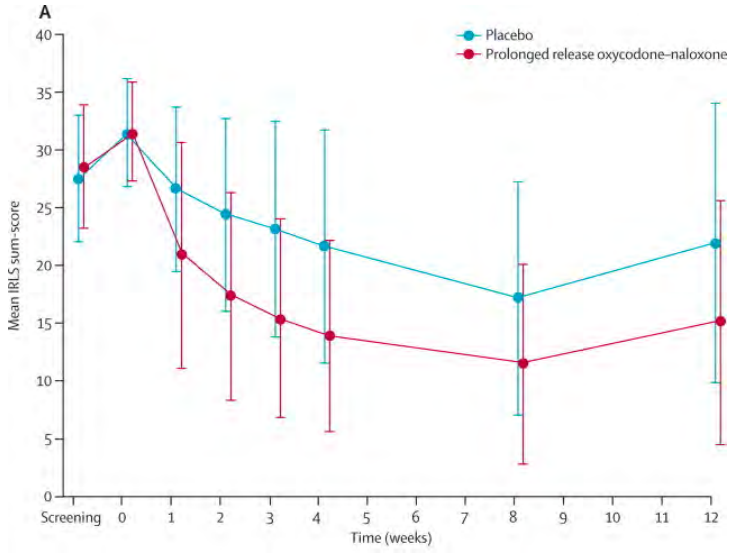
Opiates



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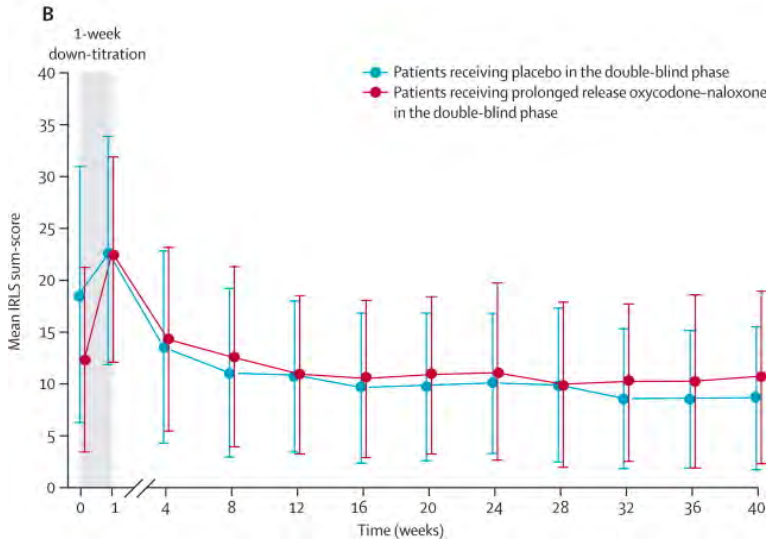
Opiates



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Opiates

- Recommendations for treatment
  - Third line agent
  - Reserved for those who have failed other agents or difficult to treat augmentation
  - Starting doses:
    - Codeine 30mg
    - Tramadol 50mg
    - Oxycodone 5mg
    - Methadone 2.5mg

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Treatment Paradigm

- Removal of offending agents may help
- Iron supplementation if ferritin <75mcg
- Use of Gabapentin, Pregabalin or Gabapentin Enacarbil as initial monotherapy
- Use of low dose dopamine agonist or dipyridamole as adjunctive therapy
  - Monotherapy if contraindication to gabapentinoid use
  - Risk of augmentation should be considered
- If all else fails, consider addition of small opiate dose

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LUNCH
EXHIBIT HALL OPEN

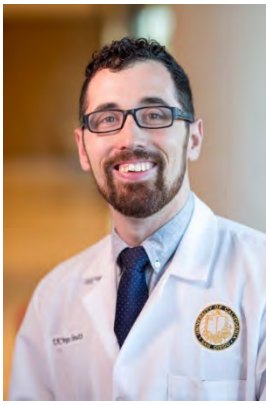
12:20 p.m. – 1:20 p.m.

Hands-On Sessions: Hypoglossal Nerve Stimulator for OSA, Neuromuscular Electrical Stimulation and Positional Sleep Therapy for OSA, Forehead Cooling for Insomnia and Actigraphy, Medical Devices for Restless Legs Syndrome

1:20 p.m. – 2:20 p.m.

GAURAV SINGH, MD, MPH
VA PALO ALTO HEALTH CARE SYSTEM
STANFORD UNIVERSITY

Dr. Gaurav Singh received his medical degree from UCSF and completed a Masters of Public Health at UC Berkeley. Currently, he is a Staff Physician at the VA Palo Alto Health Care System in the Section of Pulmonary, Critical Care, and Sleep Medicine. He is also an Affiliated Clinical Assistant Professor at Stanford University, where he completed training in Internal Medicine, followed by Pulmonary and Critical Care fellowship as well as Sleep Medicine fellowship. Dr. Singh has been involved with CTS since 2018 and has been a speaker for the Northern California Annual Conferences in 2019 and 2020. He served on the planning committee for the cancelled CTS Northern California Annual Conference in 2021. He is Conference Co-Chair for the 2022 CTS Annual Educational Conference.



BRANDON NOKES, MD
UC DAVIS

Dr. Brandon Nokes is a Pulmonary/Critical Care Physician at UCSD. He is a T32 fellow as well as an ATS ASPIRE fellow mentored by Atul Malhotra. He also runs the hypoglossal nerve stimulation clinic at VA San Diego. His research interests are in upper airway physiology, control of breathing, negative effort dependence, as well as tailoring sleep treatments to individual physiology and sleep apnea endotypes.

MICHELLE CAO, DO
STANFORD UNIVERSITY SCHOOL OF MEDICINE

Dr. Michelle Cao is a Clinical Associate Professor in the Division of Pulmonary, Allergy, and Critical Care Medicine, and the Division of Sleep Medicine, at the Stanford University School of Medicine. She is board certified in Pulmonary, Critical Care, and Sleep Medicine. Her clinical expertise is in complex sleep-related respiratory disorders, central sleep apnea syndromes, and home mechanical ventilation. Dr. Cao is the CTS president for 2022-2023.

MICHELLE PRIMEAU, MD
SUTTER HEALTH SAN CARLOS

Dr. Michelle Primeau obtained her medical degree from Case Western Reserve University in Cleveland, OH. She completed a residency in Psychiatry, but in her first year found the field of sleep medicine and was enamored. She completed her fellowship in Sleep Medicine at Stanford, as well as a post-doctoral research fellowship in sleep and mental health. In 2014, she came to Sutter Health/Palo Alto Medical Foundation and started the Sleep Wellness Program, integrating a full behavioral sleep medicine program throughout the Bay Area by training MDs, PAs, NPs and LCSWs to perform Cognitive Behavioral Therapy for Insomnia within their departments. Her clinical aim is the holistic approach to sleep medicine, integratingevaluation of lifestyle, circadian influences, as well as other physiologic disorders (OSA, RLS) for achieving sleep wellness.

RAFAEL ZUZUARREGUI, MD
SAN FRANCISCO HEALTH CARE SYSTEM
UC SAN FRANCISCO

Dr. Rafael Zuzuárregui is Director of the San Francisco PADRECC and Assistant Professor of Neurology at University of California San Francisco (UCSF). He is board certified in Neurology and fellowship-trained in Movement Disorders and Sleep Disorders. Dr. Zuzuarregui earned his medical degree, completed his residency in Neurology, served as Chief Resident, and completed his Movement Disorders Fellowship at Boston University School of Medicine. He also completed his Sleep Disorder Fellowship at Stanford University School of Medicine. Dr. Zuzuárregui's clinical focus is in the treatment of Movement Disorders and various sleep disorders, as well as the use of Botox and Deep Brain Stimulation (DBS). His research is on the intersection between movement and sleep disorders with particular focus with the impact of DBS on various sleep parameters.

Hypoglossal Nerve Stimulation (HGNS) Cheat Sheet

Manufacturer/Device: Inspire Medical Systems/Inspire (only FDA-approved HGNS device for OSA)
Others: LivaNova aura6000 (under investigation), Apnex Medical (did not meet efficacy standards for phase III study)

Indication: OSA with positive airway pressure intolerance (inability or unwillingness to use it)

Inclusion criteria:
Age: 18-65 y/o
BMI: < 32-35 kg/m^2
OSA severity: moderate to severe (15 events/hr ≤ AHI ≤ 65 events/hr)
Lack of concentric airway collapse by drug-induced sleep endoscopy (DISE)

Contraindications: Central + mixed apneas > 25% of total AHI, any anatomical finding that would compromise performance of upper airway stimulation, neuromuscular disease compromising upper airway control, unable to operate remote, pregnancy, certain models not MRI compatible, implantable devices that may be susceptible to unintended interaction with the Inspire system

Components:
Patient: implantable pulse generator (IPG, with sensing lead to intercostal muscle and stimulation lead to tongue), remote
Provider: programmer (physician tablet and wireless telemetry system)

Mechanism: Sensing lead detects inhalation and exhalation; device/generator coordinates stimulation with breathing; stimulation cuff protrudes tongue and opens airway by providing stimulation during inhalation

Protocol: Confirmation of moderate to severe OSA → Evaluation by Sleep ENT, including DISE → implantation of device, with overnight observation → evaluation by Sleep ENT in few days for wound healing → activation after 1-2 months → gradual patient titration of settings for 1 month → check-in appointment in 1 month → in-lab PSG for titration of settings to fine tune settings and evaluate efficacy in 3 months → continued gradual patient titration of settings

Activation:
1. Physical exam: Check incisions, functional tongue exam (for neurapraxia – delay activation for few months if present)
2. Use physician tablet and telemetry system to connect to generator
3. Record stimulation thresholds: start at 0.1 V and increase by 0.1-0.2 V at a time
    a. Sensation Threshold: patient first feels stimulation (mild tugging sensation in throat or tongue; average 1.2 V)
    b. Functional Threshold: tongue moves forward (up to or past lower teeth; average 1.8 V)
4. Other adjustable settings: Start Delay (30 min), Pause Time (15 min), Duration (8 hr)
5. Adjust stimulation: set amplitude to Functional Threshold (FT), Lower Limit to FT, Upper Limit to FT + 1.0 V (depending on comfort)
6. Check sensor waveforms: verify rise and fall during inhalation and exhalation, respectively, for 3 min; save screenshot; ensure comfort and lower amplitude if needed
7. Sleep remote education: app, training video, verify patient knows how to use remote → step up amplitude by 1 setting (0.1 V) every few nights (~ every 3 nights)
8. Other settings: Electrode (default = [+ - +]), Pulse Width (μs), Rate (hz)

Remote basics:
- Status ring: White (therapy off), solid green (therapy on, stimulation on), dimming/brightening green light (therapy on, stimulation paused)
- Buttons: green (turn on, pause), grey (turn off), increase + (increase stimulation), decrease – (decrease stimulation) – push button then bring up to generator until hear beep; stimulation strength gauge on back of remote

Tips:
- Comfort is critical to success, step down amplitude for few days if uncomfortable (can provide few levels to go down at activation)
- No rush, can increase amplitude at individualized pace to allow acclimation, but encourage use all night and every night
- Provide expectations regarding the process (therapeutic benefit may not occur immediately, maximal benefit will take time)

Selected Readings:
Strollo PJ Jr et al. N Engl J Med. 2014 Jan 9;370(2):139-49. – STAR Trial, AHI 29.3 → 9.0, ESS 11 → 6 after 12 mo
Woodson BT et al. Otolaryngol Head Neck Surg. 2018 Jul;159(1):194-202. – Sustained improvement in AHI, ESS, QoL after 5 yr
Mashaqi S et al. Int J Environ Res Public Health. 2021 Feb 9;18(4):1642. – Recent review of HGNS

CTS 2022 – Transoral neuromuscular stimulation (ExciteOSA) cheat sheet

Indications:
Mild OSA and snoring (not tested in more severe SDB)

Instructions:
User titrated settings based on tolerability (1-15 on associated app). Apply mouthpiece to tongue and use for 20 minutes daily for 6 weeks. Maintenance therapy is 2x per week thereafter (not rigorously assessed thus far).

Device settings:
The voltage delivered by the eXciteOSA is tailored towards the patient's tongue resistance. The patient has complete control of the intensity of therapy which ranges from 1-15. Depending on the tongue resistance of the patient (calculated by the induction current at the start of the therapy), the patient will receive any way between 1.35v at level 1 to 29V at level 15.

Monitoring:
Adherence and user settings are monitored on the device app as well as a cloud-based monitoring system.

Side effects:
Drooling, tongue tingling.

Mechanism of activity:
Putatively genioglossus stimulation (based on prong location), shown to increase tongue endurance.

Payment:
Not insurance eligible
Is available through Veterans Affairs
HAS/FSA eligible
$1650 through DME companies

References:
Appended below:

Reference studies:

	Wessolleck *et al*[1] *Somnologie*, 2018	**Kotecha *et al*[2]** *Sleep & Breathing*, 2021	**Baptista et *al*[3]** *Journal of Clinical Medicine*, 2021	**Nokes *et al*[4]** *Under review*	**Nokes *et al*[5]** *Under review*
Study Design	Single-center, single-arm trial	Multi-center, single-arm trial			Single-centre, single-arm trial
Study Sample	n=13 (AHI<15)	n=70 (AHI<15) Subset: Interim analysis	n=115 (AHI<15) Full participant sample	n=65 (AHI 5-14.9) Subset: Mild OSA only	n=20 (AHI<15 during screening sleep test; PSG then performed for research)
Country	Germany & UK	UK	UK & Spain	UK & Spain	USA
Duration	Six weeks treatment Home sleep test at baseline	Six weeks treatment Two home sleep tests pre- and post			4-6 weeks treatment PSG pre- and post
Change in AHI (events/hr)	Not captured	Mild OSA subset: -5.1 /hour (from 9.8 to 4.7)	Not reported for mild OSA subset	Mild OSA: -3.4 /hour (from 10.2 to 6.8)	Mild OSA subset: -11.3 /hour (from 19.7 to 8.4)
Change in ESS (0-24 points)	Not captured	Mild OSA subset: -3.9 /24 (from 9.0 to 5.1)	Not reported for mild OSA subset	Mild OSA: -3.4 /24 (from 8.7 to 5.3)	Not reported for mild OSA subset
Other outcomes	Bed-partner reported snoring ↓44%	Objective snoring >40dB ↓41%; Bed-partner reported snoring ↓39%			Self-reported sleep quality improvement (PSQI; p=0.03)
Device usage / adherence	Not captured	83% (percentage of days the device was used)			86% (percentage of days with ≥1 session)

Ebb CoolDrift Versa

WHAT?
A novel, forehead cooling device, delivering “frontal cerebral thermal therapy”
- cooling 4°C to 16°C (57– 61°F)

WHERE? Available direct to consumer on Amazon, CPAP.com for $399
(Without Rx)

- replace components (fluid cartridge, headband) every 6 months
- Amazon rated 4.1/5

WHY?

- **Rationale:** Hyperarousal has long been hypothesized to underlie insomnia symptoms; and persistent elevation of frontal lobe overactivity (metabolism) has been shown to correlate with sleep disturbances. This device purports to reduce frontal lobe activity via cooling mechanism.

  - **Roth/ Nofzinger: RCT, 106 pts, v placebo (vestibular stimulation system).**
    - **No statistically significant difference on primary endpoints (latency to persistent sleep, sleep efficiency)**
    - **However, % change was significantly different, as was latency to N1/N2**
    - **No serious adverse effects (most common headache, but reading Amazon reviews, also skin irritation)**
    - Note large placebo effect

- Additional company sponsored data demonstrates:
  - 30 pts, over 4 weeks time:
    - reduced ISI (19.7—> 9.4)
    - SL (43—>20.7 min)
    - WASO (63—> 24.5 min)
    - Replicated in Veterans (2)
    - No adverse effects at 6 mo (3)

Roth T, Mayleben D, Feldman N, Lankford A, Grant T, Nofzinger E. A novel forehead temperature-regulating device for insomnia: a randomized clinical trial. Sleep. 2018;41(5): zsy045. doi:10.1093/sleep/zsy045

Schirm, J. Bellamy, B.' Nofzinger, E.: EFFICACY OF DIRECT THERMOELECTRIC FOREHEAD COOLING FOR TREATING INSOMNIA SYMPTOMS. SLEEPJ (43) supplement 2020; Nofzinger, E.EFFICACY OF A FOREHEAD-COOLING DEVICE FOR TREATING INSOMNIA IN VETERANS. SLEEPJ (43) supp 2020; Rippole, D. Schirm, J., Nofzinger E. DURABILITY OF EFFECTS OF FOREHEAD COOLING ON EEG SLEEP MEASURES IN INSOMNIA PATIENTS FROM SLEEPJ (43) supp

Restless leg syndrome wearables “Cheat sheet”

1) Restiffic
    a. Device: Adjustable foot wrap with compressive pad
    b. Justification: Found to significantly improve RLS symptoms in 8 week trial (n=30) with 1 week washout at week 5. Mean IRLS reduction by 17.22 reduction overall.
    c. Indication: treatment of moderate to severe restless legs syndrome when inactive
    d. Mechanism of action: presumed sensory input to peripheral nerves via gentle pressure to the feet
    e. Adjustments: Uses a hook and loop systems to allow for adjustment of pressure on medial and planter aspect of feet
    f. Contraindications: neuropathy, poor circulation, peripheral vascular disease, previous or active deep vein thrombosis, leg swelling
    g. Price: $199 pre-shipping and tax
    h. Not covered by insurance, may be able to submit for reimbursement to private insurance

2) Pneumatic compression device
    a. Device: Adjustable compression device with variable intensity levels of pressure
    b. Justification: Found to significantly improve RLS symptoms in 4 week trial (n=35). Mean IRLS reduction from 14.1 (3.9) to 8.4 (3.4) overall.
    c. Indication: treatment of mild to moderate restless legs syndrome
    d. Mechanism of action: presumed increase in local perfusion and/or release of enthothelial mediators
    e. Adjustments: Handheld controller to allow for adjustment of pressure settings on legs and/or feet
    f. Contraindications: skin infection, vein ligation, previous or active deep vein thrombosis, anatomical deformity of the leg
    g. Price: variable, $50-100
    h. May be covered by insurance as DME, may also be able to submit for reimbursement to private insurance

ACTIGRAPHY

WHAT?
Movement tracking, also usually monitors ambient light exposure.

- long used in research and some clinical contexts
- Validated, published algorithms for sleep v wake
- FDA-cleared, Medical Grade

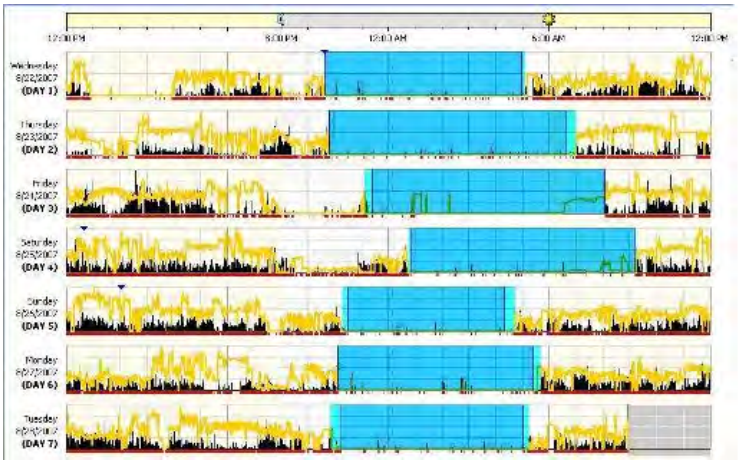
WHERE?
Respironics Actiwatch Spectrum Plus (usa.phillips.com)

WHY?

- billable: code 95803 (RVU 2021: 4.62; not covered by CMS)
  - Actigraphy, testing, recording, analysis, interpretation and report (requires the patient to wear a home monitor for 24-hours a day for 3 to 14 days)

- Best use for confirming diagnosis (circadian rhythm disorders, insufficient sleep, use with home sleep testing or tracking pre-MSLT), or clinical decision making (nonresponse to cognitive behavioral therapy for insomnia, patient requests increased hypnotic dose, patient reporting is of questionable validity), but conditional recommendation by AASM (1)
  - Can differentiate those with insomnia v without (2)
  - Insomnia:
    - generally Actigraphy differs from sleep logs pre-treatment (total sleep time (TST), sleep latency (SL), sleep efficiency (SE)) but agrees with PSG (TST, SL). Performs worse for wake after sleep onset (WASO).
    - Post-treatment, Actigraphy agrees more with logs, but not consistently with PSG

- AASM also has a statement regarding the use of consumer sleep wearables



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Wildfires and Effects on Obstructive Airways Diseases

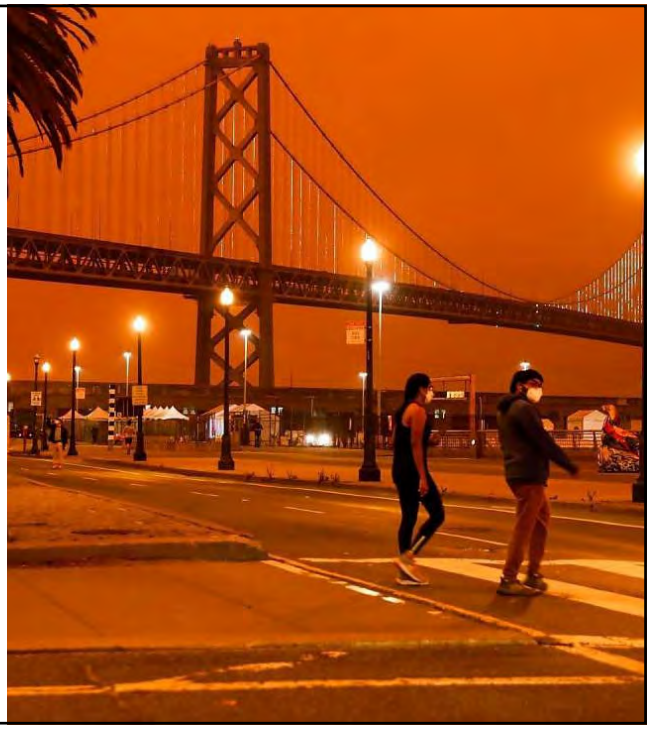
2:20 p.m. – 3:05 p.m.

NEETA THAKUR, MD
UC SAN FRANCISCO

Dr. Neeta Thakur received her MD and MPH from the University of Arizona and completed advance training in Clinical Research and Implementation Science. Her work centers on improving asthma and COPD care delivery for individuals from high-burdened communities and addressing social factors, such as early life adversity, to reduce the disease burden. Dr. Thakur applies methods from social epidemiology and implementation science to illuminate the barriers that prevent patients with COPD and asthma from receiving best-practice care. She has successfully implemented programs that improve access to evidence-based interventions adapted for low resource safety-net settings.

Wildfires and Effects on Obstructive Airways Disease

Neeta Thakur, MD MPH
@nthakurMD
March 12, 2022



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Disclosures

- No relevant financial relationships with a commercial interest
- 2018-current Chair of the American Thoracic Society Health Equity and Diversity Committee
- Funding: NHLBI, PCORI, RWJF, CA Office of the Governor, Genentech Corporate Giving

2

Questions to answer

Why are we seeing an increase in wildfire events in the United States?

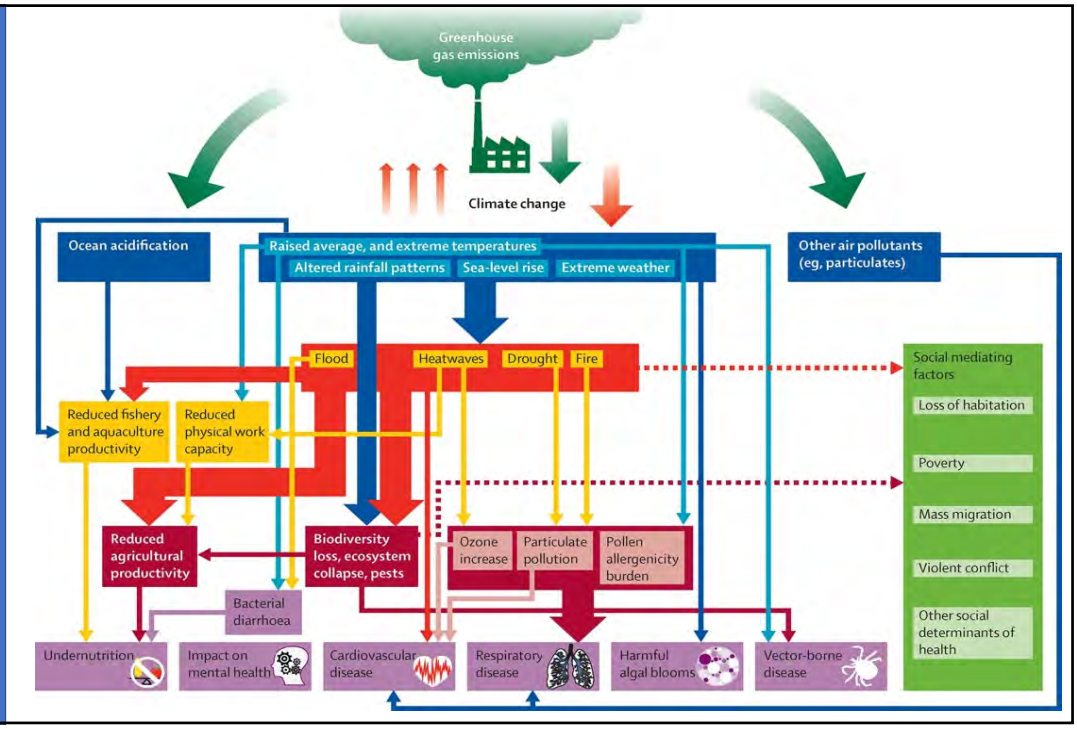
What are the respiratory health effects of wildfire smoke events? ← Who is at greatest risk?

What works and what to tell our patients with COPD?

3

Overview of links between greenhouse gas emissions, climate change and health.

(Watts, Lancet Commission, 2020)



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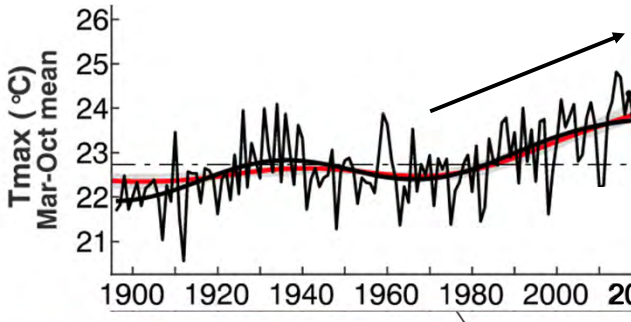
What is needed for a wildfire?

Fuel

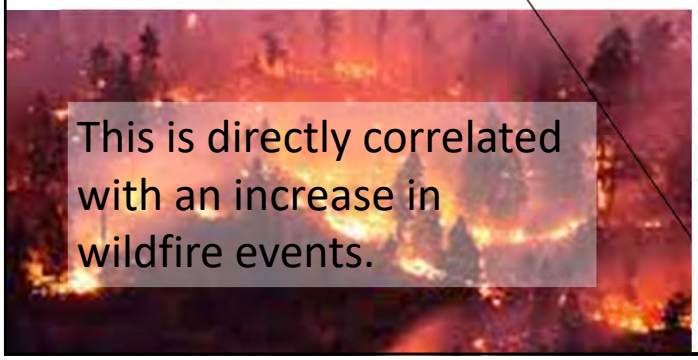
Heat

Oxygen

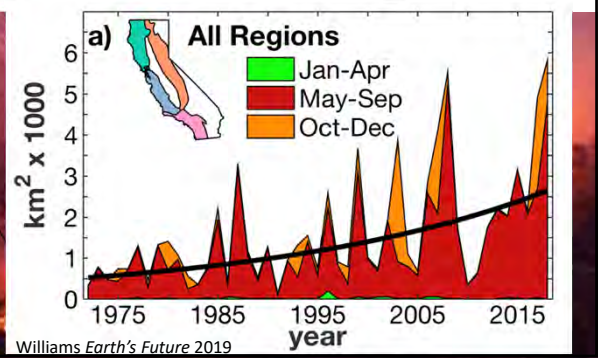
5



We've observed a clear upward trend in temperature over the last 5 decades.



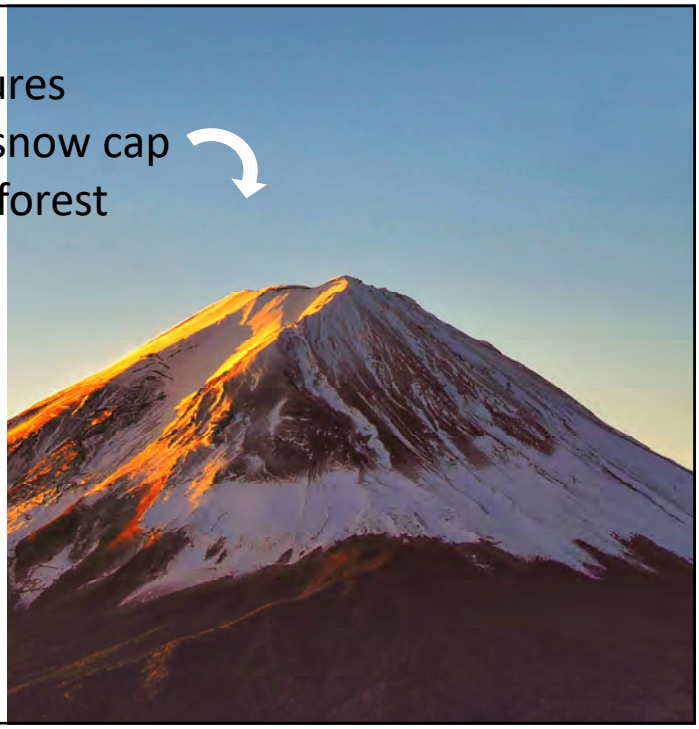
This is directly correlated with an increase in wildfire events.



Williams *Earth's Future* 2019

6

Warmer temperatures
earlier melting of snow cap
more, shrub, drier forest



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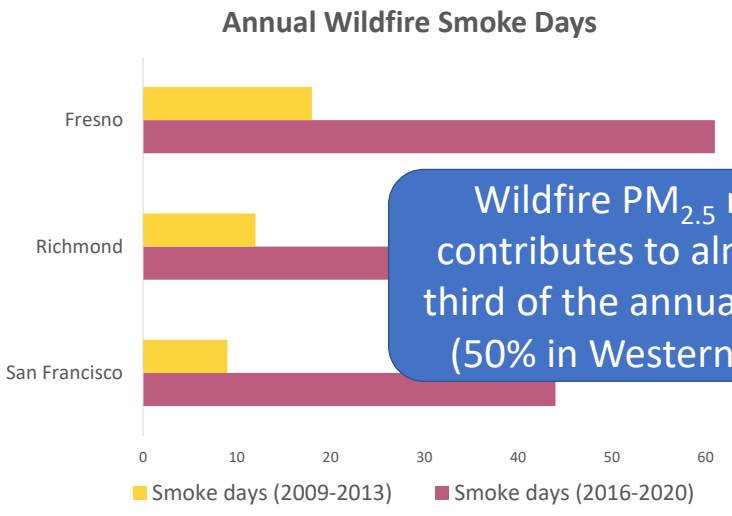
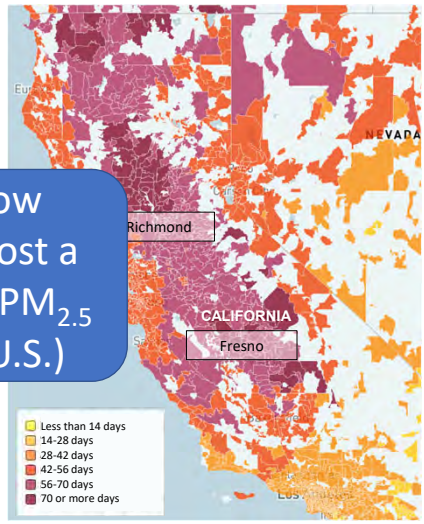


Wildfire $PM_{2.5}$ now contributes to almost a third of the annual $PM_{2.5}$ (50% in Western U.S.)

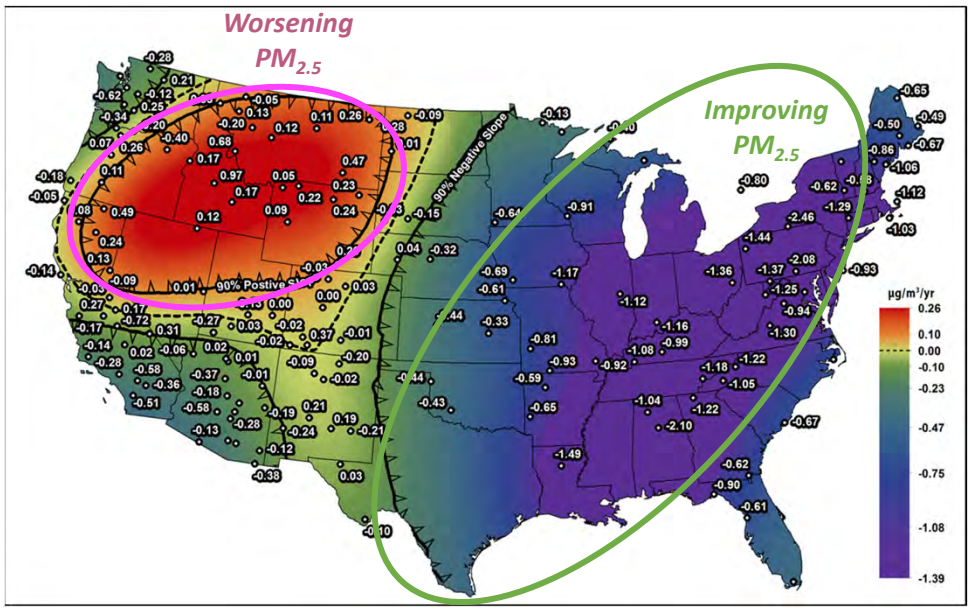


www.capradio.org;
EPA Federal Emissions Inventory 2014

8

$PM_{2.5}$ Air Quality Improved 1988-2016

Except in Wildfire-Prone Areas

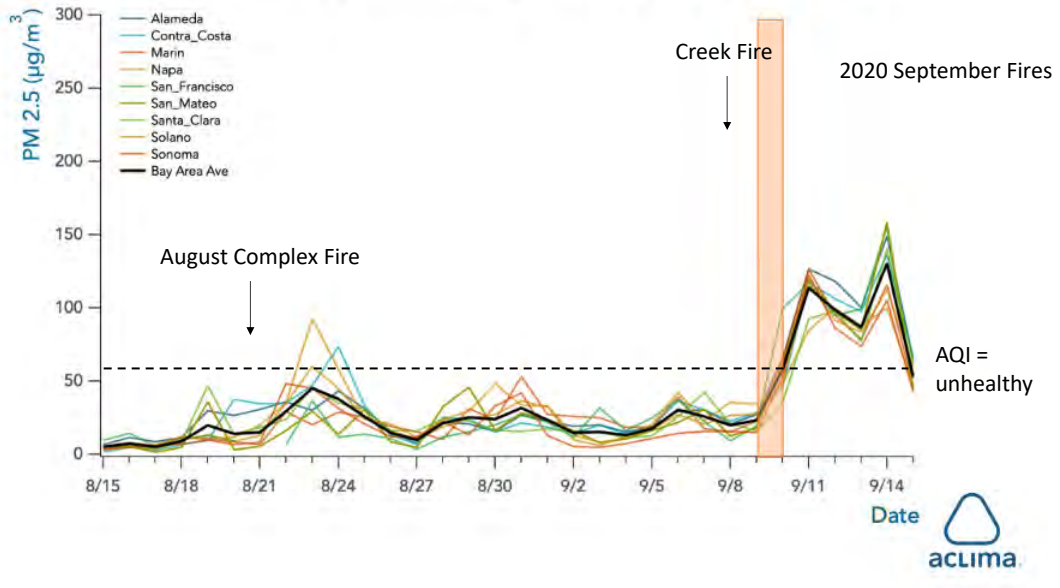


Slide credit: MB Rice

McClure and Jaffe. *Proc Natl Acad Sci.* 2018

9

Bay Area Daily Average $PM_{2.5}$ by County



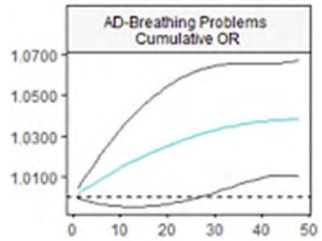
10

More Ambulance Calls for Respiratory Problems within Hours of Smoke

Data for 2010–2015 wildfire seasons in British Columbia

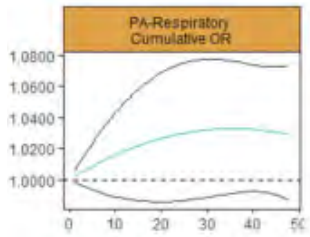
Ambulance Dispatches for "Breathing Problems"

OR



Paramedic Assessment: Respiratory Problem

OR



OR in association with a 10 μg/m^3 increase $PM_{2.5}$ in the lag period of 1–48 h

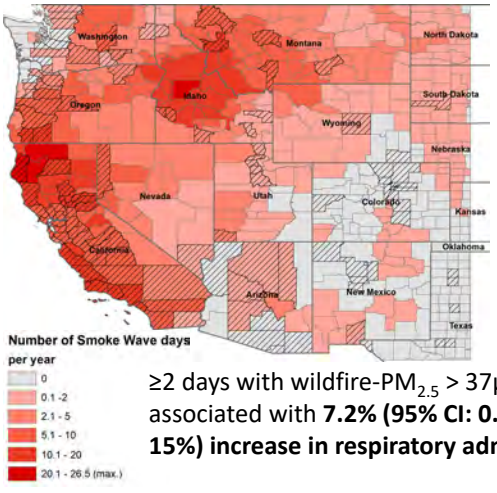
Slide credit: MB Rice

Yao et al. *Environ Health Perspect* 2020

11

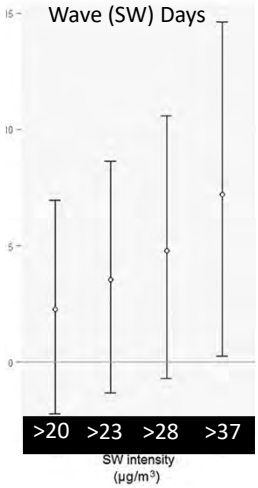
Wildfire-Specific $PM_{2.5}$ and Respiratory Hospitalization of Medicare Patients

Wildfire-specific $PM_{2.5}$ was estimated using a global chemical transport model



≥2 days with wildfire-$PM_{2.5}$ > 37μg/m^3 associated with **7.2% (95% CI: 0.25%, 15%) increase in respiratory admissions**

% Increase in Respiratory Admissions on Smoke Wave (SW) Days

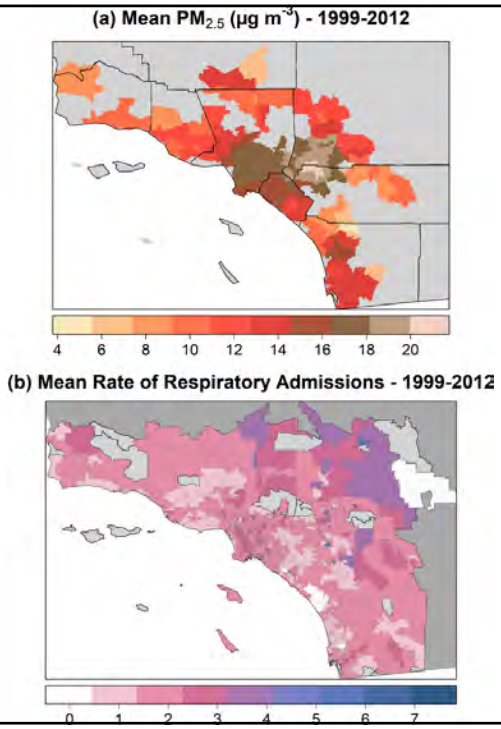


Liu et al. *Epidemiology*. 2017

Slide credit: MB Rice

12

Wildfire $PM_{2.5}$ is associated with increased respiratory-related hospital admissions



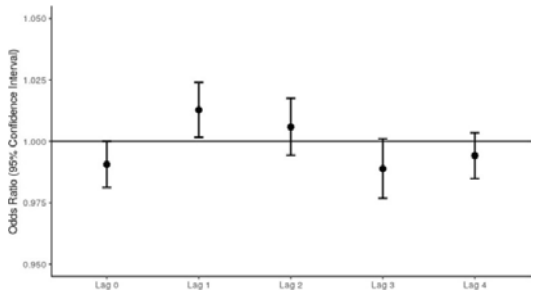
Aguilera Nature Comm 2021

13

Odds of Mortality Highest in COPD

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs)

Category	Lag Day 0: Adjusted OR (95% CI)
All non-traumatic	1.01 (0.99, 1.04)
Underlying cause of death	
Cardiovascular	0.99 (0.94, 1.04)
Ischemic heart disease	1.04 (0.93, 1.17)
Respiratory	1.09 (1.00, 1.18)
Asthma	0.51 (0.23, 1.12)
COPD	1.14 (1.02, 1.26)*
Pneumonia	1.08 (0.86, 1.36)
Cerebrovascular	0.90 (0.75, 1.07)



Doubleday Environmental Health 2020

14

Characteristics that increase risk of poor health

15

Socially vulnerable populations

"characteristics of a person or community that affect their capacity to anticipate, confront, repair, and recover from the effects of a disaster"

or in this case…Wildfire Smoke Events

Adapted from CDC Definition
Flanagan J Environ Health 2018

16

Vulnerability

- Poverty
- Housing (inc. lack of)
- Race/Ethnicity
- Very young – Very old

17

Susceptibility

Individual

Prevention

Macro

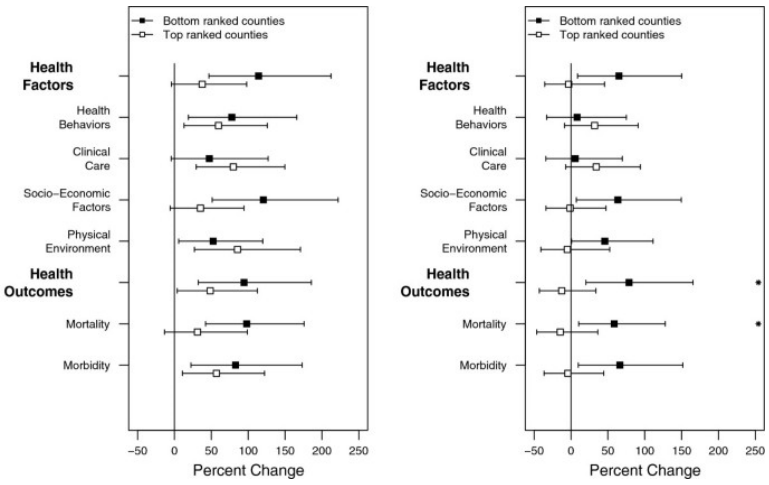
Hallegatte. Poverty and climate change: introduction. Environment and Developing Economies. 2018

18

Susceptibility

Community vulnerability changes risk of hospitalization for asthma.

Percent Change in Relative Risk of Asthma-related ED visits in Eastern North Carolina



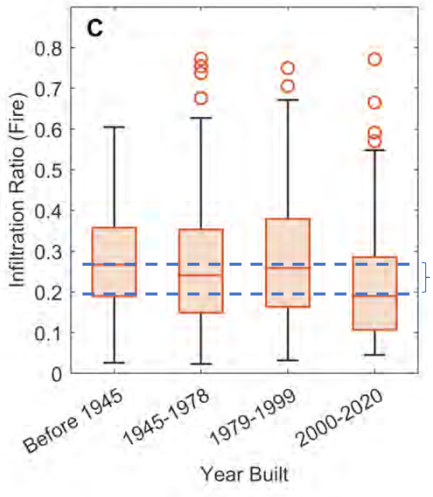
Counties ranked on: healthy behaviors, SES, physical environment, care access, and mortality/morbidity

Rappold Environmental Health 2012

19

Prevention

Wildfire Smoke penetration based on housing stock

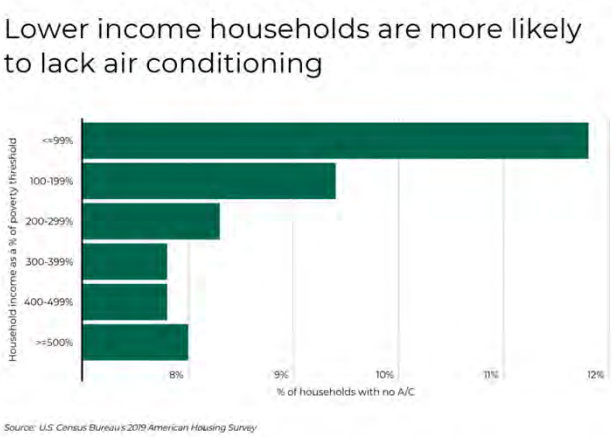


P=0.004

1400 insi
sensors a
counterp

Housing
mandate
mechani
systems

Mitigation Strategies

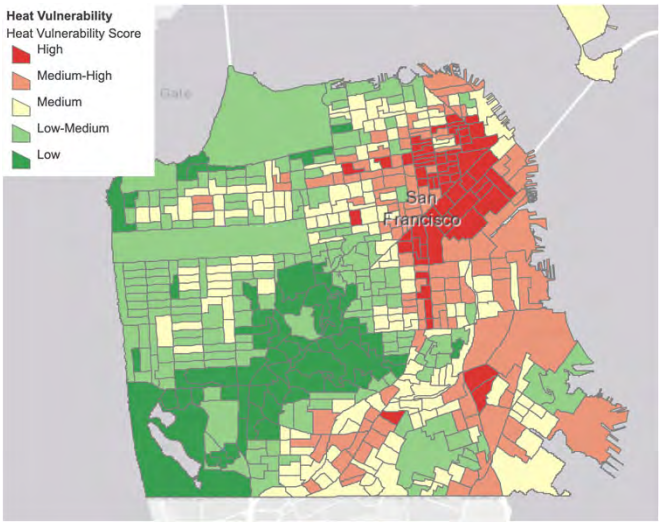


Liang PNAS 2021

20

Identifying communities at risk

SFDPH Heat Vulnerability Index

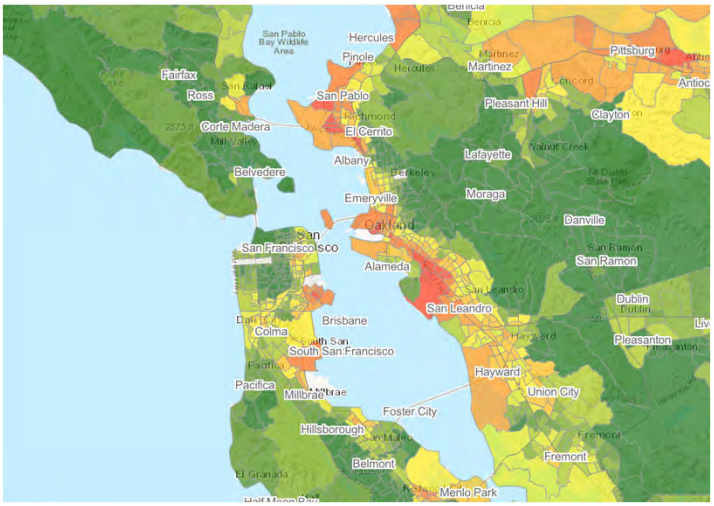


21

Identifying communities at risk

CalEnvironScreen4.0

https://oehha.ca.gov/calenviroscreen/report/calenviroscreen-40

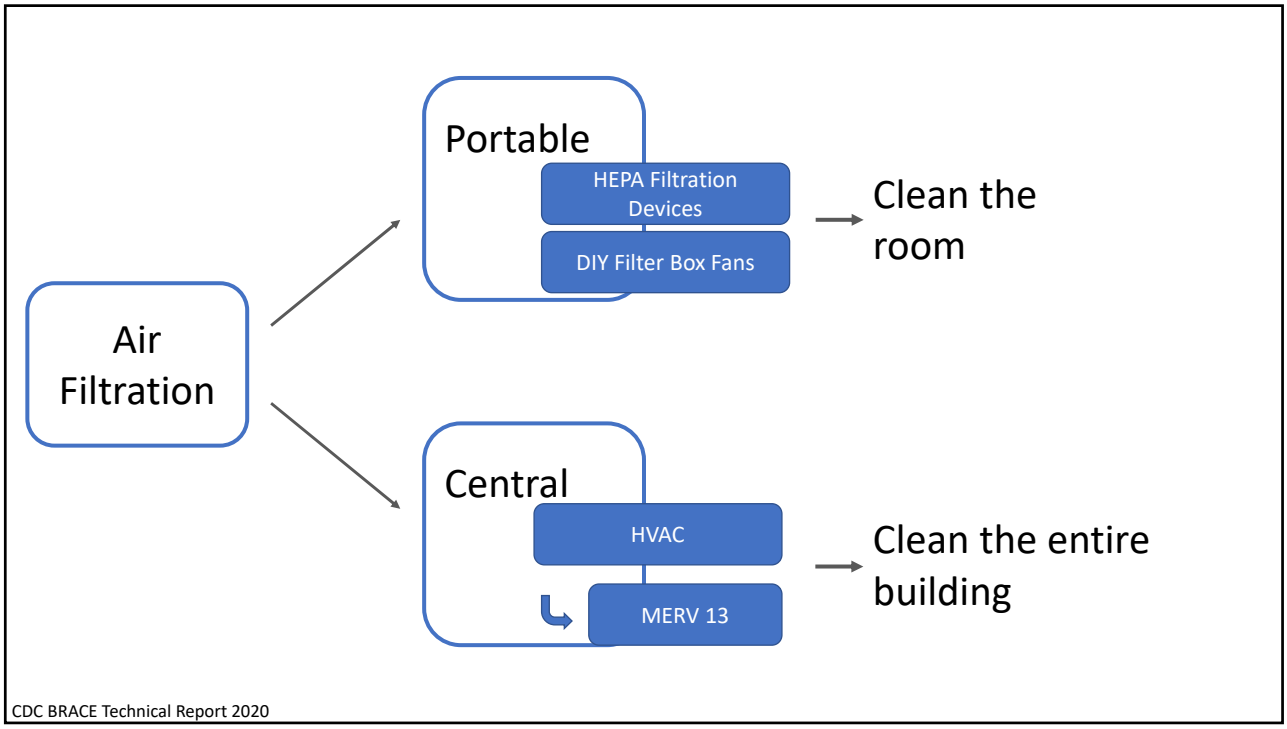


22

Strategies

- Household HEPA Air Cleaners
- Low-cost DIY Box Filtration Fans
- Respirators
- Weatherization

23



CDC BRACE Technical Report 2020

24

Filter type

- The type of filter matters
- MERV ≥13 removes smoke
  - HEPA are MERV 16

MERV Ratings (ASHRAE Standard 52.2)[86]

MERV RATING	PARTICLE SIZE RANGE (μM)	EFFICIENCY	APPLICATION
1–4	3.0–10.0	<20%	Minimum Equipment Protection
5–8	3.0–10.0	≥20% to <85%	Minimum Particulate Protection Residential Homes Commercial Buildings
9–12	3.0–10.0 1.0–3.0	≥85% <50 to ≥80	Improved Particulate Protection Industrial Buildings Commercial Buildings Residential Buildings
13–16	3.0–10.0 1.0–3.0 0.30–1.0	≥90% >90% <70 to ≥95	Superior Particulate Protection Smoke Removal Healthcare Facilities General Surgery

CDC BRACE Technical Report 2020

25

HEPA Filters reduce Indoor PM2.5 by 30-80%

Sample home during Summer Wildfire event

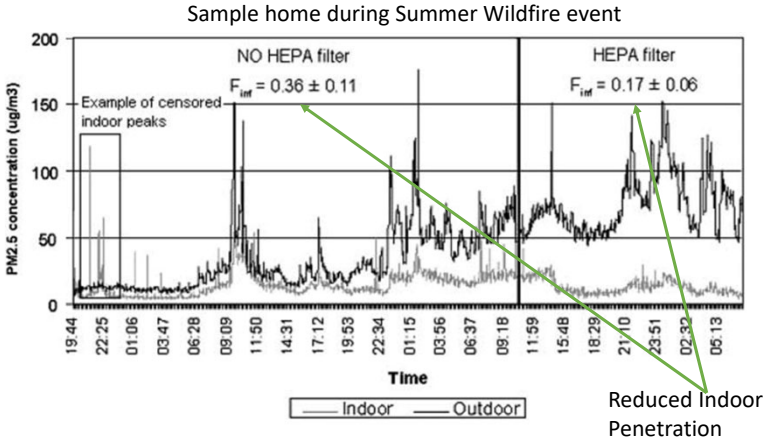



Photo of HVAC units.

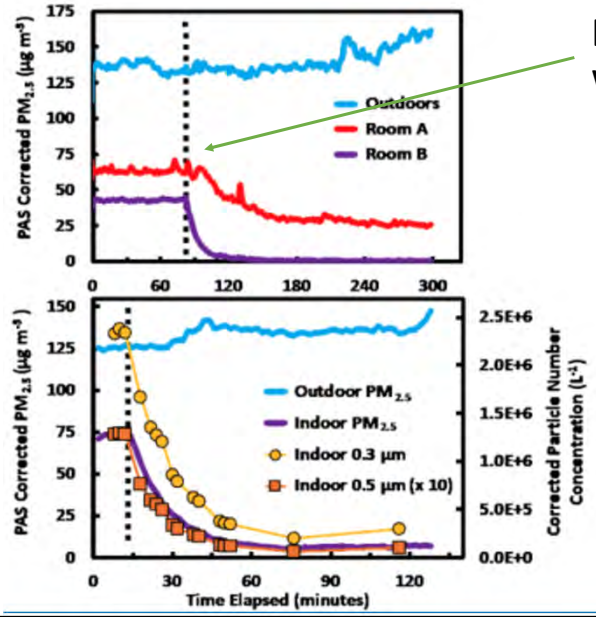

Photo of a portable air cleaner.

- HEPA filters effectively reduce penetration of outdoor $PM_{2.5}$
- Likely reduce adult respiratory symptoms during wildfire events (limited evidence)

CDC BRACE Technical Report 2020; Barn Journal of Exposure Science and Environmental Epidemiology 2008; Mott J West Med. 2002

26

DIY Box Fans



Effective at reducing Wildfire $PM_{2.5}$

27

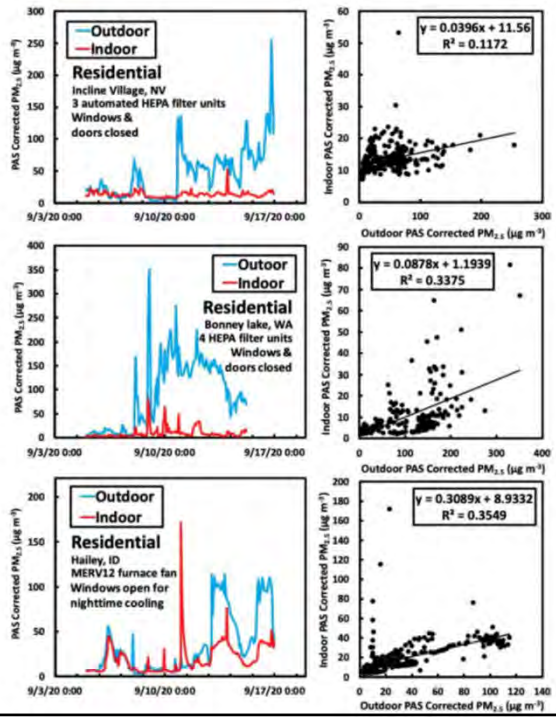
DIY Box Fans

Dependent on use

Home 1:
3 AUTO devices, windows and doors closed

Home 2:
4 devices (turn on/off), windows and doors closed

Home 3:
1 box filter, windows open at night



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Respirators (e.g. N95)

- Reduce exposure to PM but not gas pollutants
- May mitigate short-term physiological effects of PM (evidence limited to healthy adults)
- None approved for children (NIOSH certifies N95s)
- Safety of prolonged use not evaluated in adults with severe heart or lung disease


Source: FEMA

Slide credit: MB Rice

Shi et al. *Environ Health Perspect.* 2017

29

Patient Communication

- Stay indoors
- Keep windows and doors closed
- Make sure air is not recycled from outside
  - If you have an HVAC system with a fresh air intake, set the system to recirculate mode, or close the outdoor intake damper.
  - If you have a window air conditioner, close the outdoor air damper. If you cannot close the damper, **do not use the window air conditioner**. (Make sure that the seal between the air conditioner and the window is as tight as possible).
  - If you have an HVAC system which has a filter, you can set the fan to continuous operation to pull indoor air through the filter, even when the HVAC system is not actively heating or cooling or when the heat/cool is intermittent. Ensure filter is MERV 13 or higher
  - If you have a portable air conditioner with a single hose, typically vented out of a window, do not use it in smoky conditions. If you have a portable air conditioner with two hoses, make sure that the seal between the window vent kit and the window is as tight as possible.
- Reduce activities that might increase pollutants (smoking, wood smoke, cooking, lighting candles)
- Do not vacuum anywhere in the house unless using a HEPA-filter equipped vacuum
- Keep the room clean (use a damp cloth or mop)
- Ventilate the room once outside air quality is improved

30

California's Community Air Protection law (AB 617, 2017)

Source: *California Air Resources Board*

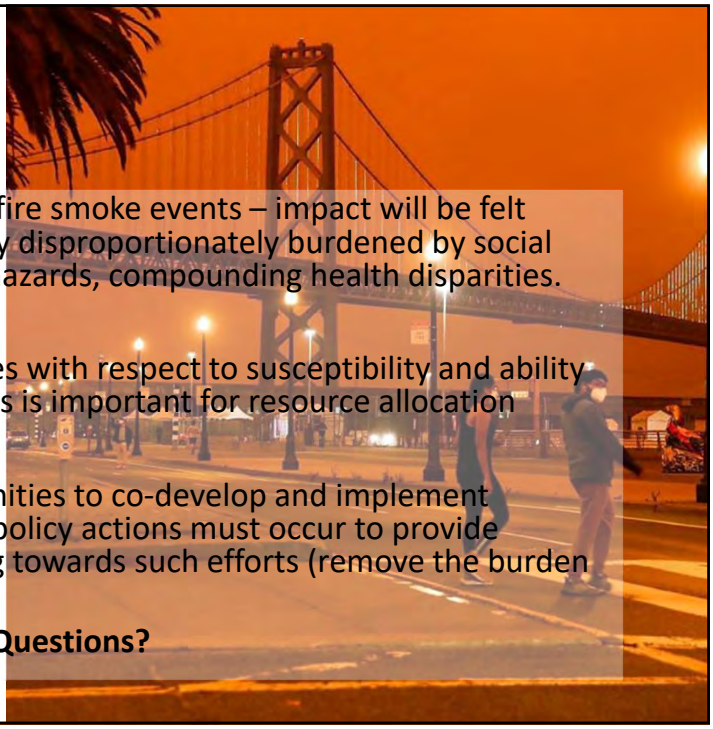
What are models for collaborative policy that puts community first?

31

Summary

- Climate change – including wildfire smoke events – impact will be felt greatest by communities already disproportionately burdened by social adversities and environmental hazards, compounding health disparities.
- Identifying high risk communities with respect to susceptibility and ability to deploy preventative strategies is important for resource allocation
- In addition to engaging communities to co-develop and implement acceptable mitigation strategy, policy actions must occur to provide adequate resources and funding towards such efforts (remove the burden from the community).

Questions?



UCSF University of California San Francisco

ZUCKERBERG SAN FRANCISCO GENERAL Hospital and Trauma Center

32

Climate Crisis: Impact on Lung and Overall Health

3:05 p.m. – 3:50 p.m.

JOSE VEMPILLY, MD
UC SAN FRANCISCO AT FRESNO

Dr. Jose Joseph-Vempilly specializes in Pulmonary & Critical Care, with an emphasis in asthma. He is board certified in Internal Medicine, Pulmonary Disease and Critical Care Medicine. Dr. Joseph-Vempilly completed his fellowship training at the Medical University of South Carolina Teaching Hospitals. His medical degree is from St. John's Medical College.

Climate Change & Health Impacts

Jose Joseph Vempilly MBBS, MD, MRCP(UK)

Professor of Medicine, UCSF

Chief of Pulmonary & Critical Care

VA Medical Center, Fresno CA

I have no financial or other COI to declare

Not receiving any consulting fee or Speaker Bureaus to pharmaceutical

Writes three chapters for UpTodate which has no bearing on todays topic

Which one of the following is true regarding Ozone?

A Ground level Ozone prevents UV radiation from the Sun reaching Earth

B Ozone layer in Troposphere protects earth against radiation from the Sun

C Ozone layer is formed in Stratosphere when Sun light breaks down Oxygen molecules

D Ground Level Ozone formed during summer can last for >24 hours

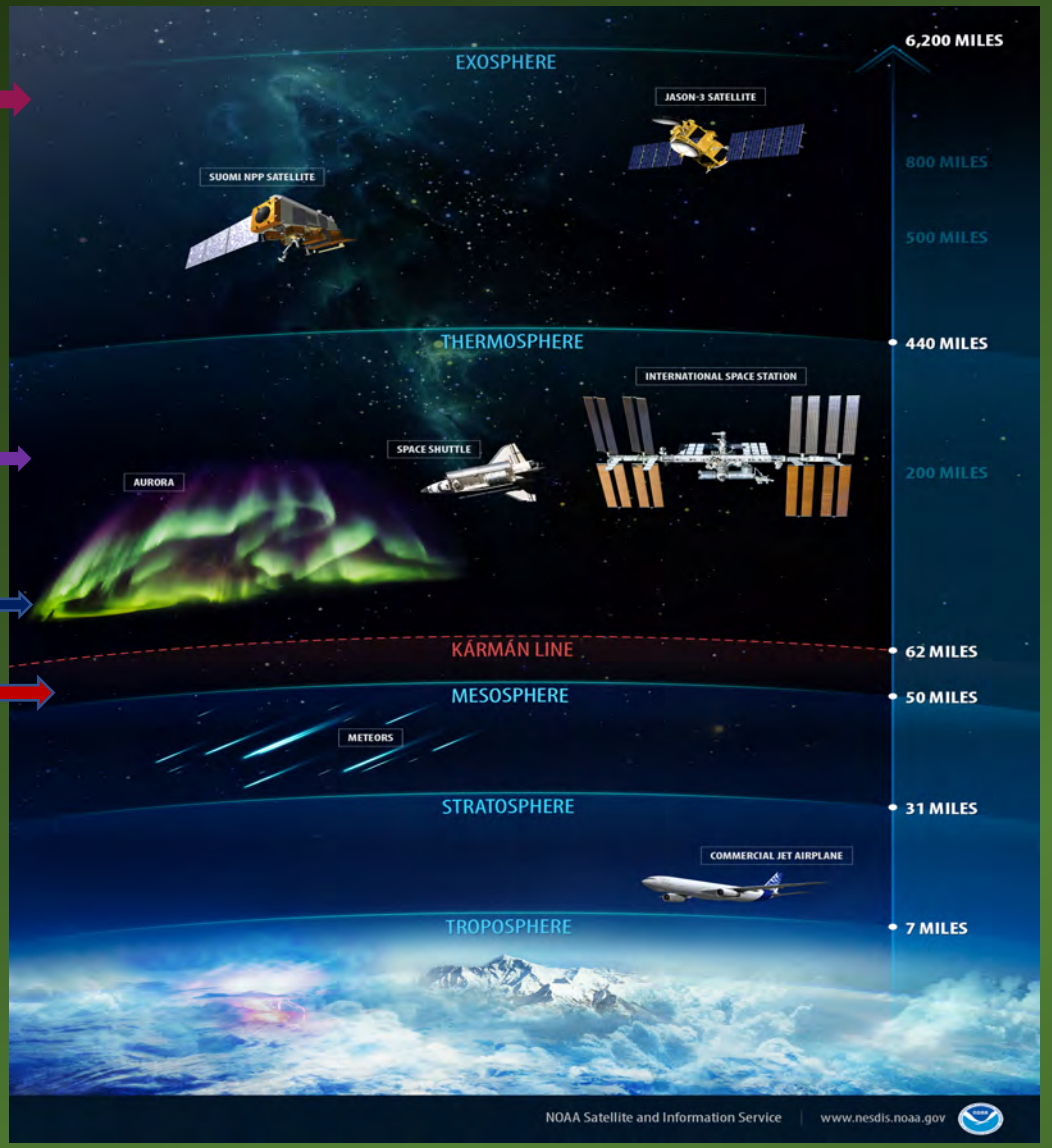
Five Layers of Protection for Mother Earth

Where no man has gone before
William Shatner

Space-x Starship

Blue Origin

Virgin Galactic



6200 miles

800 miles

500 miles

440 miles

200 miles

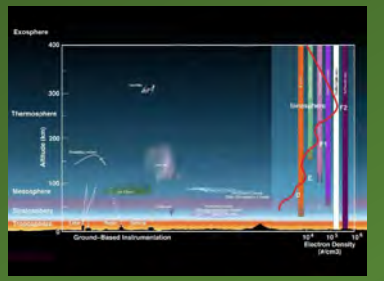
62 miles

50 miles

31 miles

7 miles

Ionosphere



Which one of the following is a strong Green House Gas?

A Chlorofluorohydrocarbon

B Hydro fluorocarbons

C Carbon dioxide

D Argon

Green House Gas Effect

Major Greene House Gas

- Water Vapor
- Carbon Dioxide
- Methane
- Nitrous Oxide
- Ozone
- Chlorofluorocarbons (CFCs)
- Hydro fluorocarbons

Which one of the following gases has the highest Raditaive Forcing to Cause Climate Change?

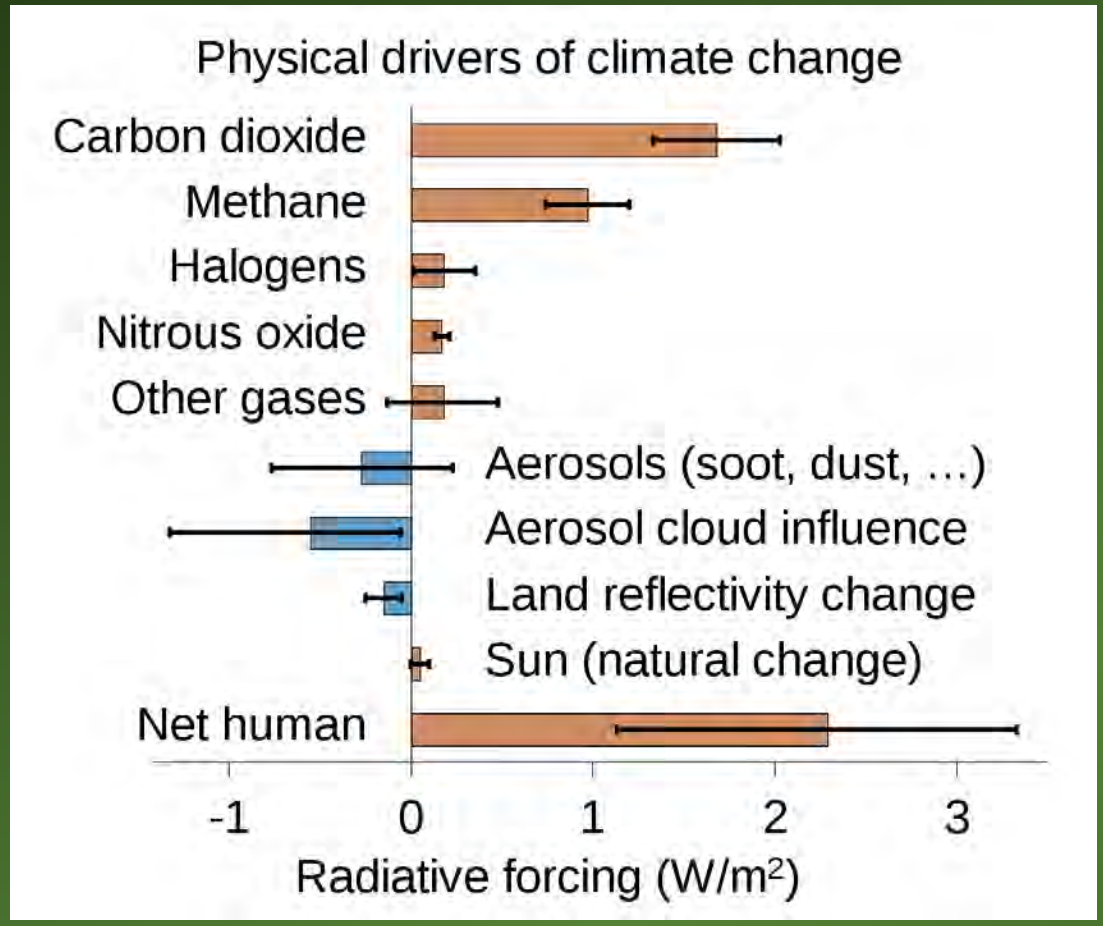
A **Carbon dioxide**

B **Methane**

C **Nitrous Oxide**

D **Halogens**

Radiative Forcing



History of Climate Science

Joseph Fourier French Mathematician (1768–1830).

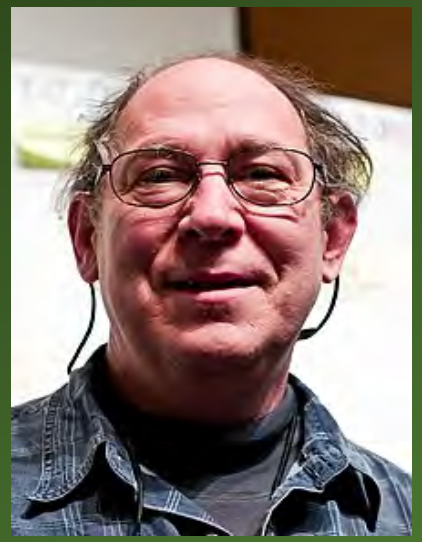
John Tyndall Royal Institute of Great Brittan 1820-1893

Svante Arrhenius 1859 -1896: University of Upsala (Nobel Price in Chemistry)

Gilbert Plass : UT at Dallas

The Doyens of Climate Science

Charles Keeling
1928 -2005
Scripps Institution of Oceanography



Stephen Schneider
1945-2010
Stanford Woods Institute for the Environment

Professor James Hanson
Earth Institute
NASA Goddard Institute of Space
Columbia University

What is Keeling Curve?

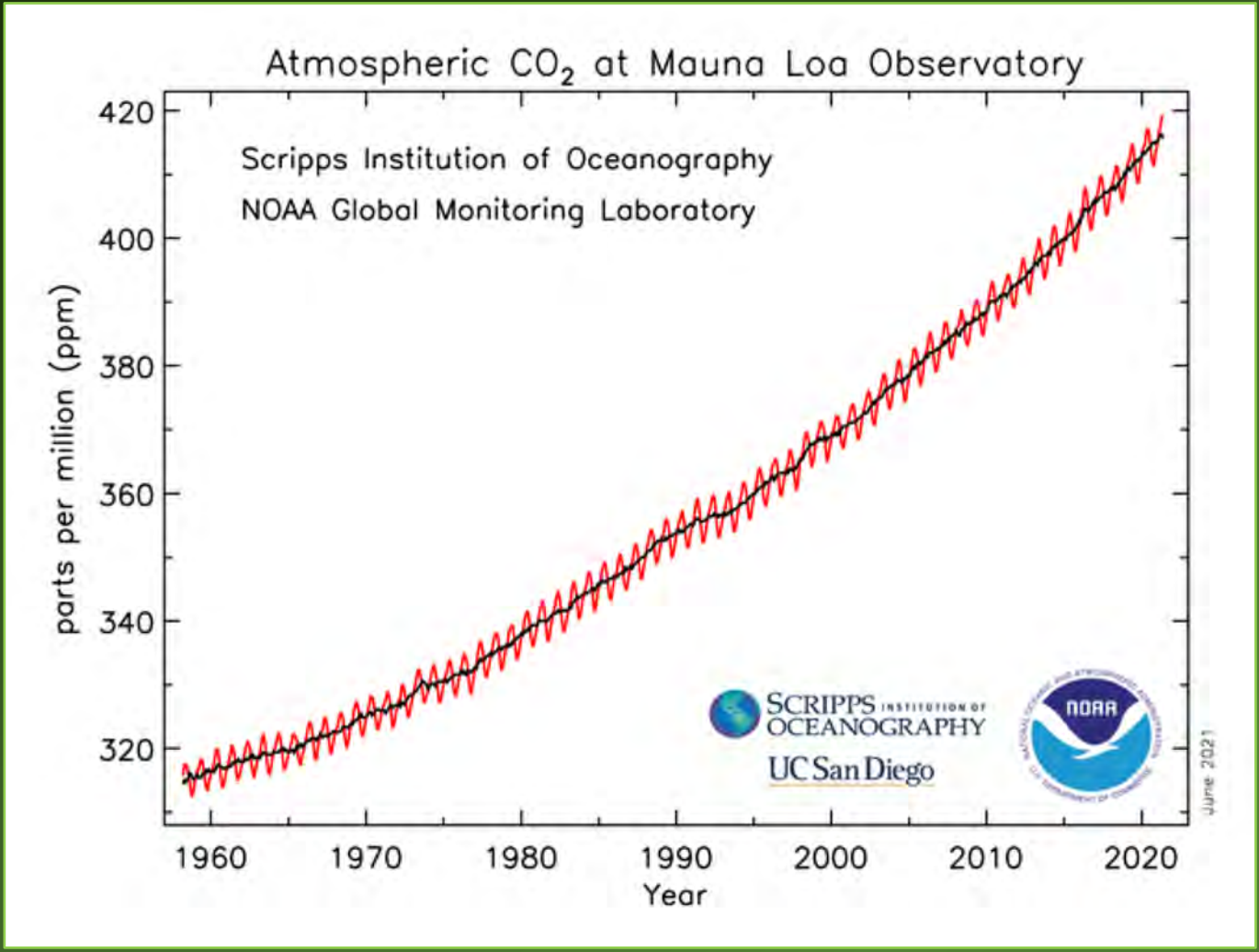
A Describes the increase in global annual Temperature

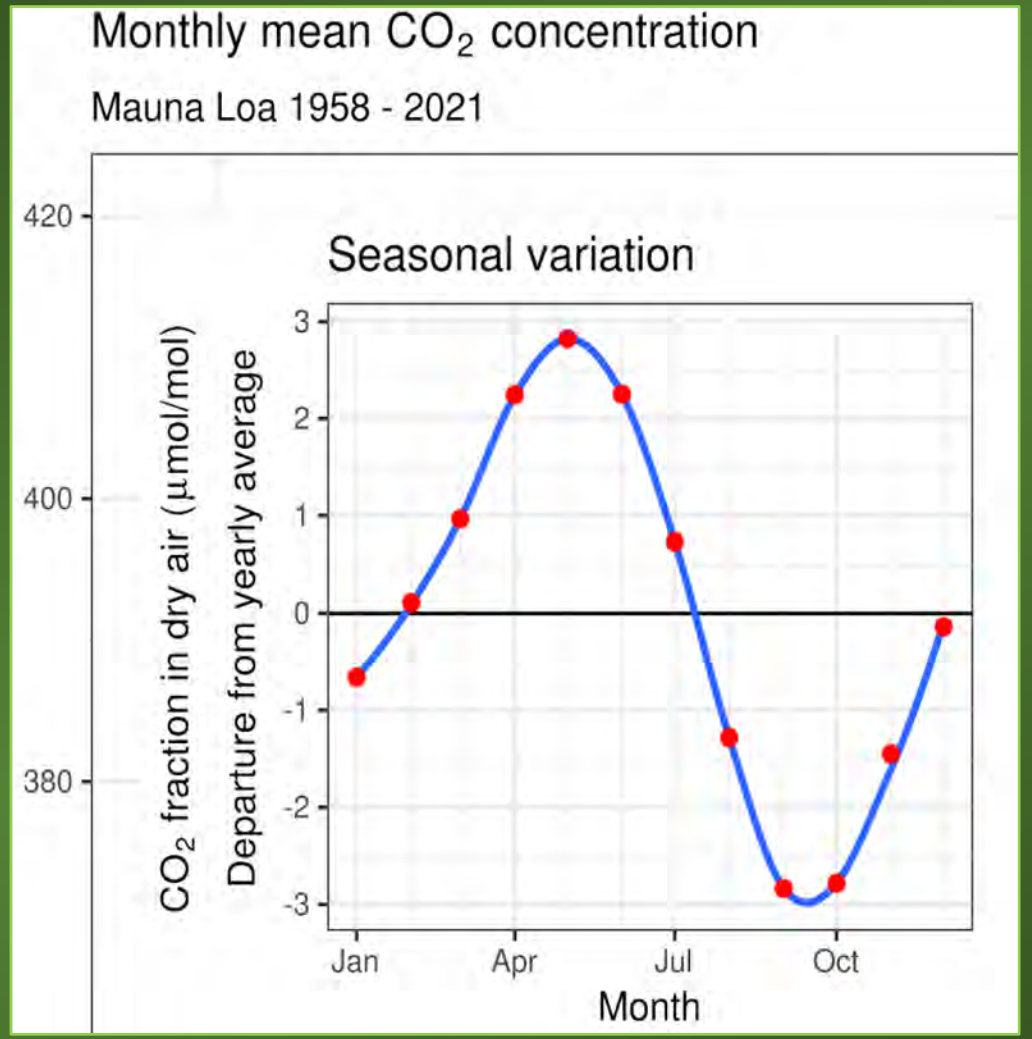
B Describes the increase in annual Methane Concentration

C Describes the increase in annual Ozone concentration in Stratosphere

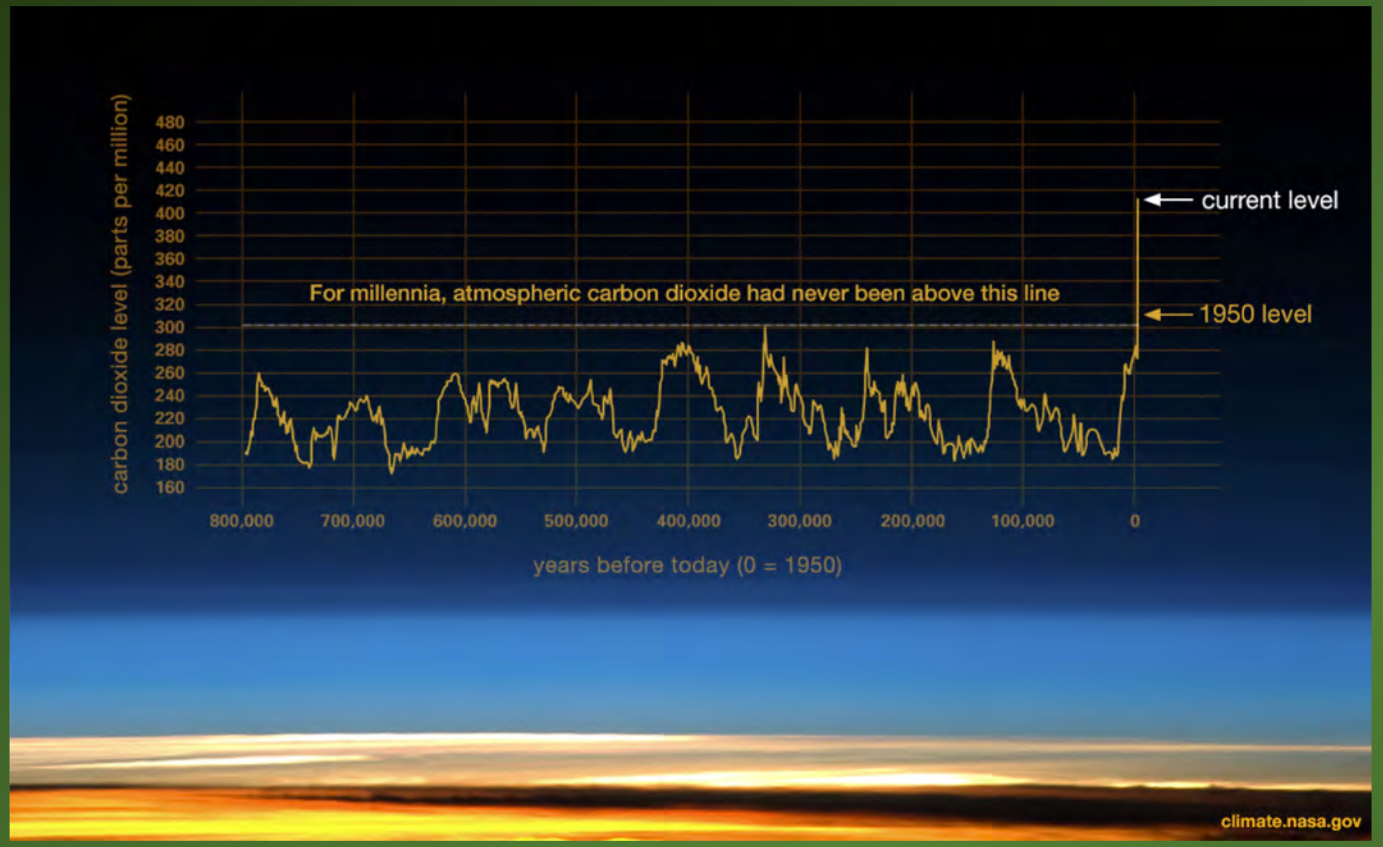
D Describes the increase in annual CO_2 concentration

There's an Esthetic to the Curve that's Beautiful Science & Troubling Reality: Charles Keeling





At no point During at least the past 800,000 Years have Atmospheric CO2 Levels been as High as They Are Now



Vostok ice core data; NOAA Mauna Loa CO_2 record Gaffney, O.; Steffen, W. (2017). "The Anthropocene equation," The Anthropocene Review (Volume 4, Issue 1, April 2017), 53-61.

Compared to Year 1880, the 12 month running average Global Surface Temperature has increased in 2020 by?

A **0.4 degree Celsius**

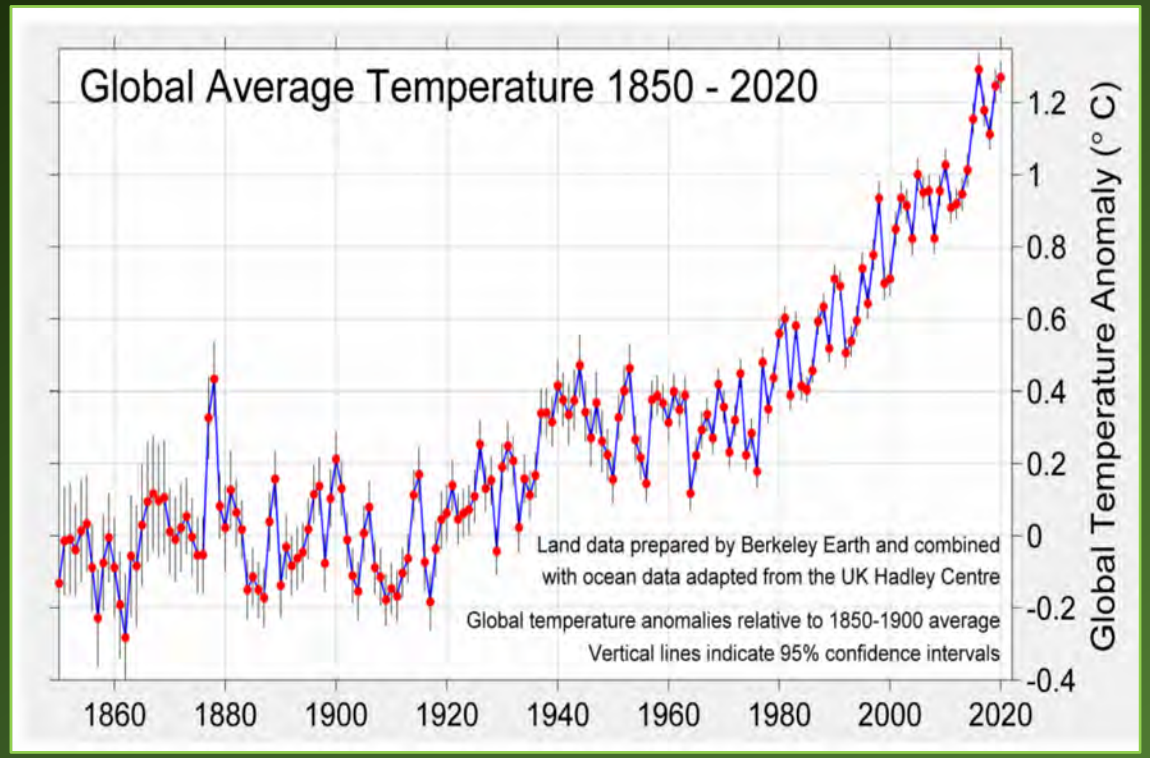
B **0.8 degree Celsius**

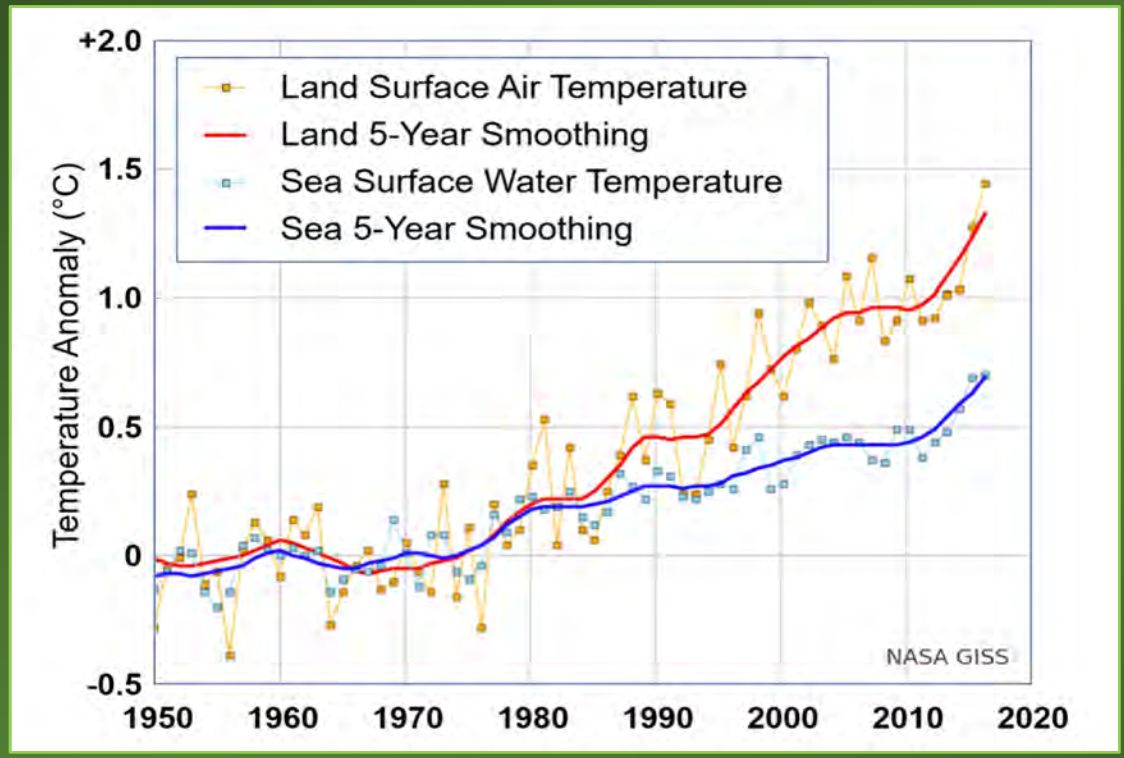
C **1.2 degree Celsius**

D **2 degree Celsius**

NASA/Berkeley Earth

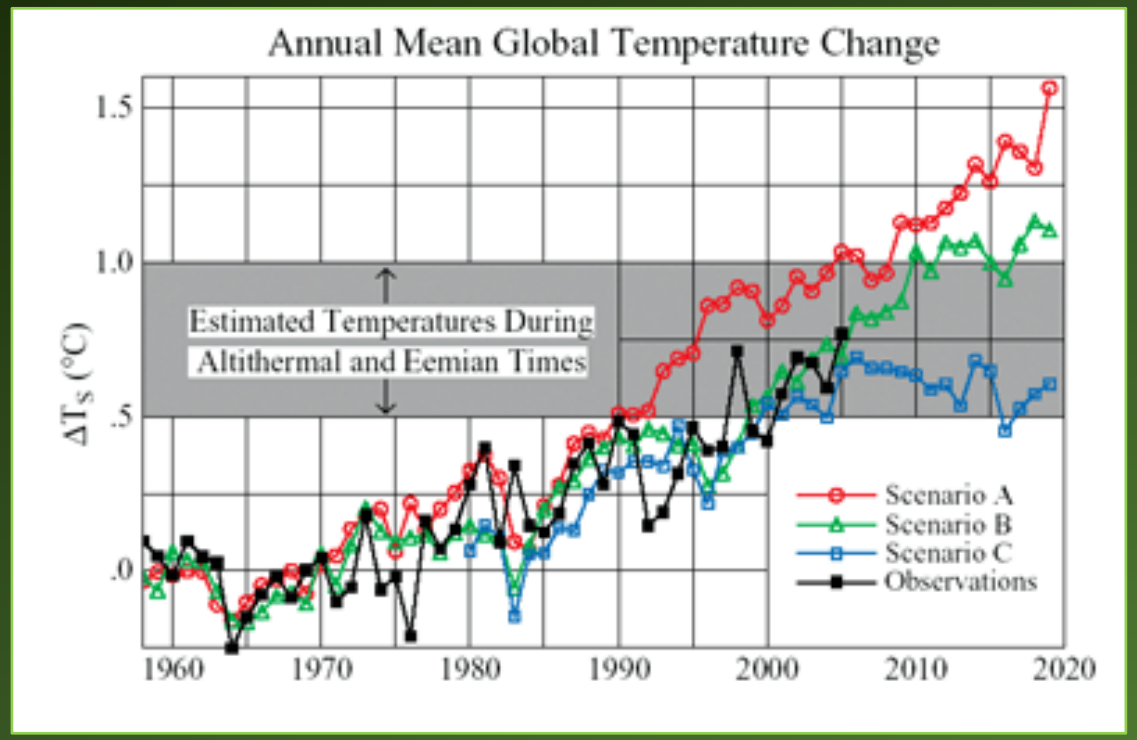
Land & Ocean Temperature Rise from Pre-industrial times: Globe is Warming

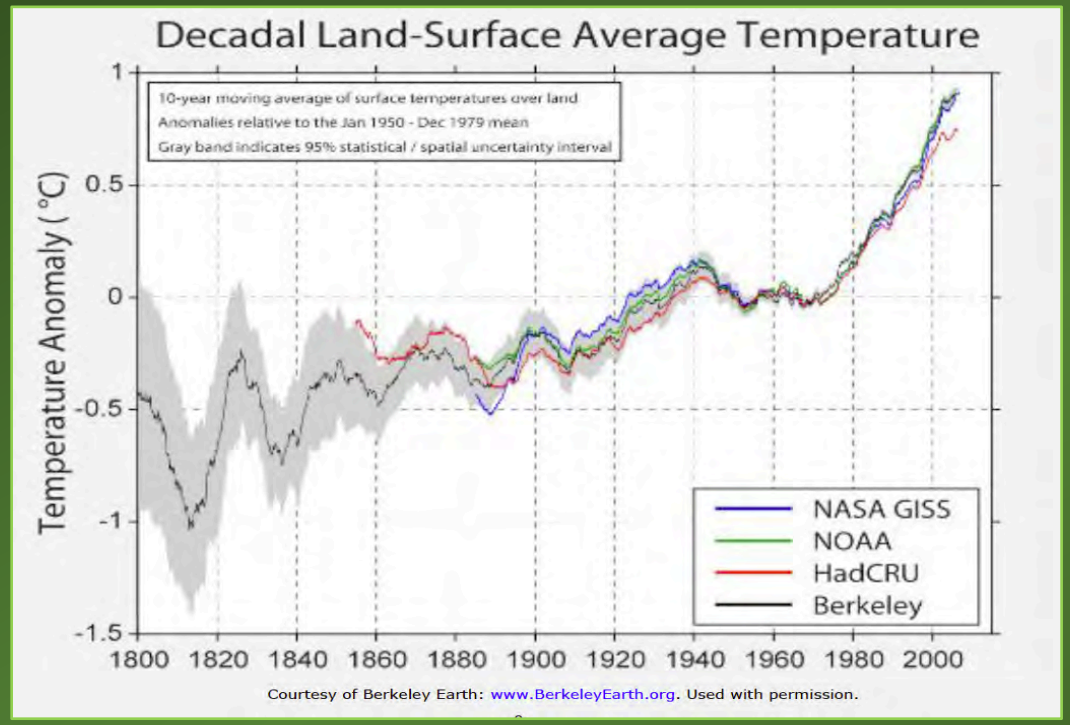




Berkeley Earth/ NASA

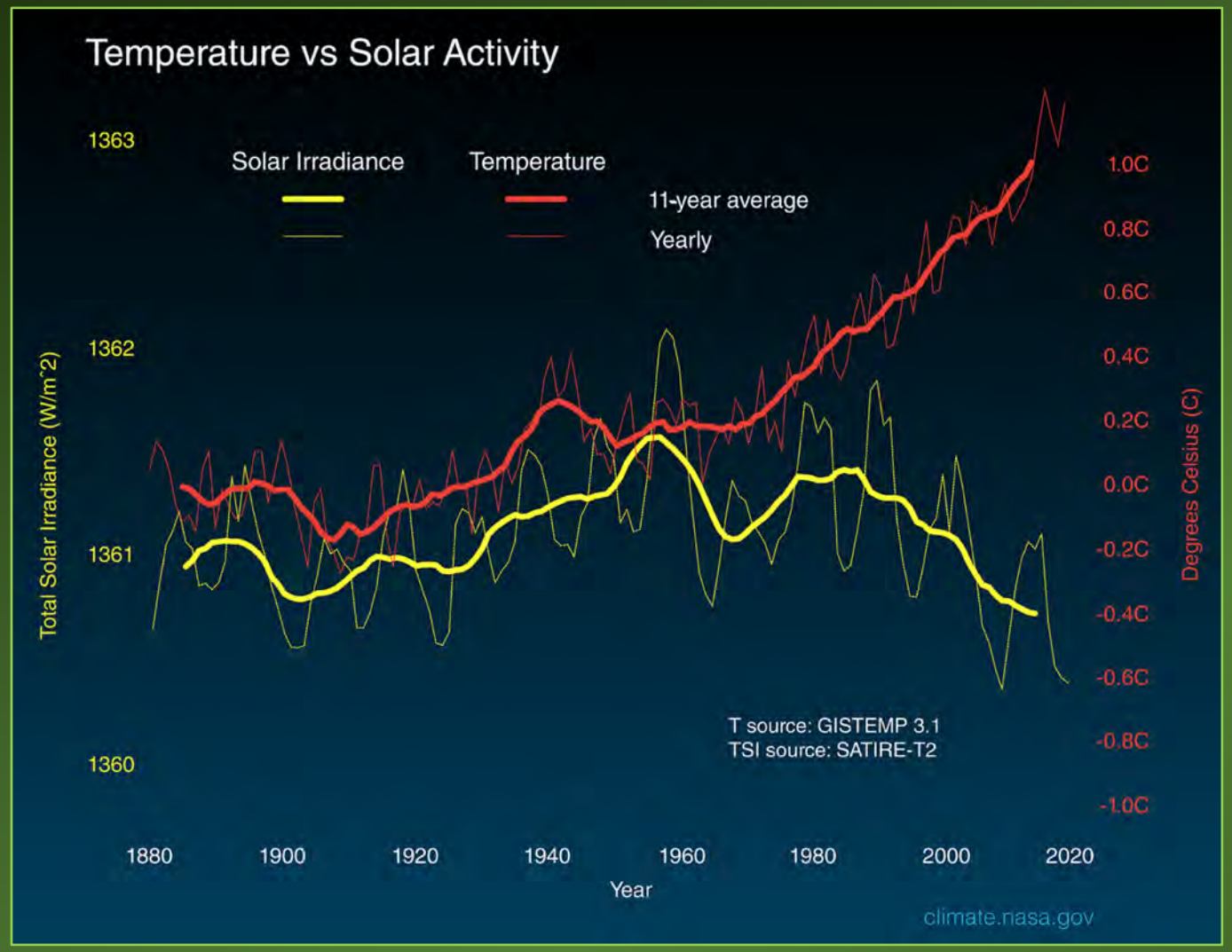
James Hansen's Testimony to Congress 1988, Has been Confirmed by Several Institutions



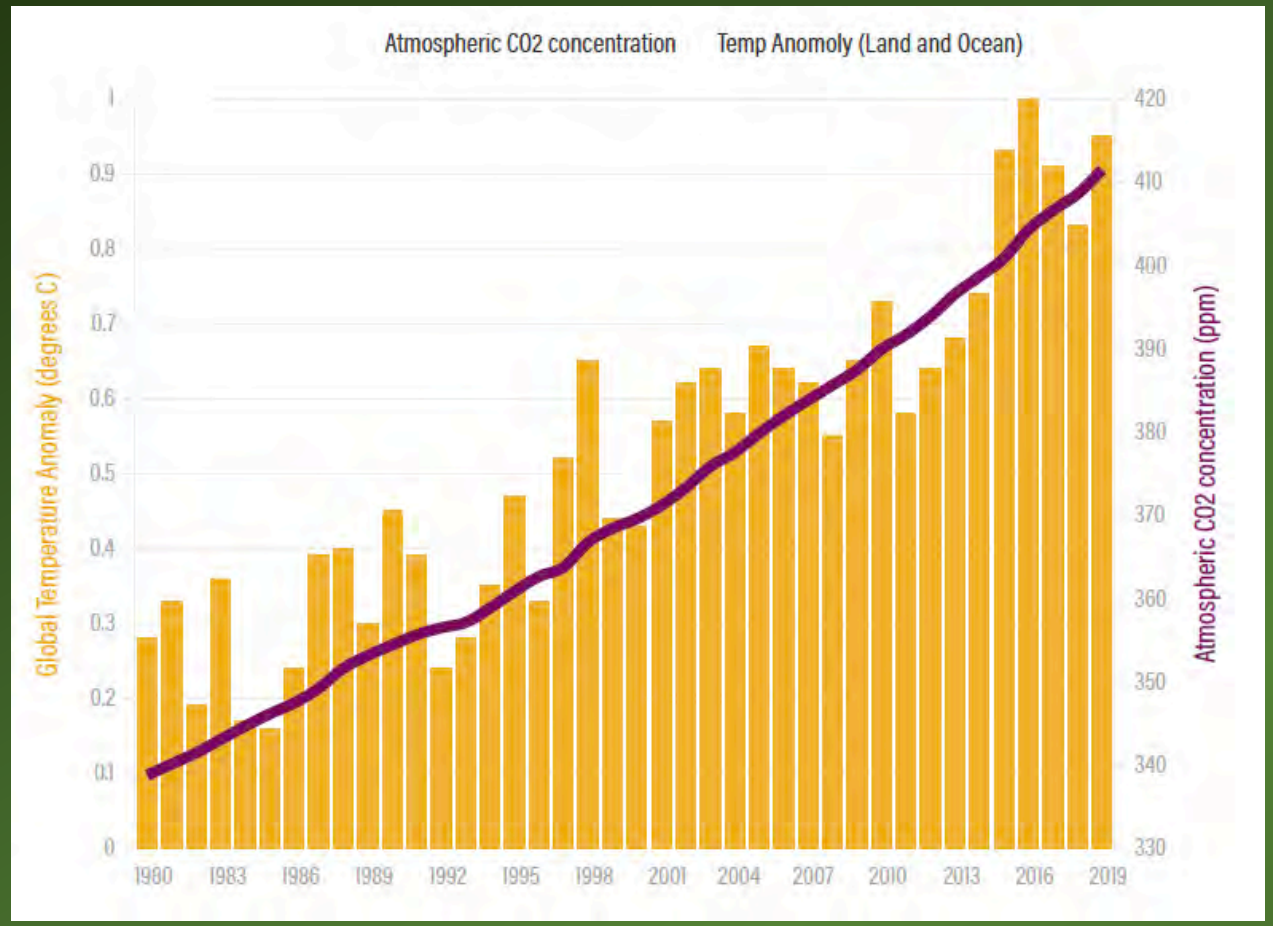


J Hansen & M Sato, 2020

Global Surface Temperature vs Solar Activity

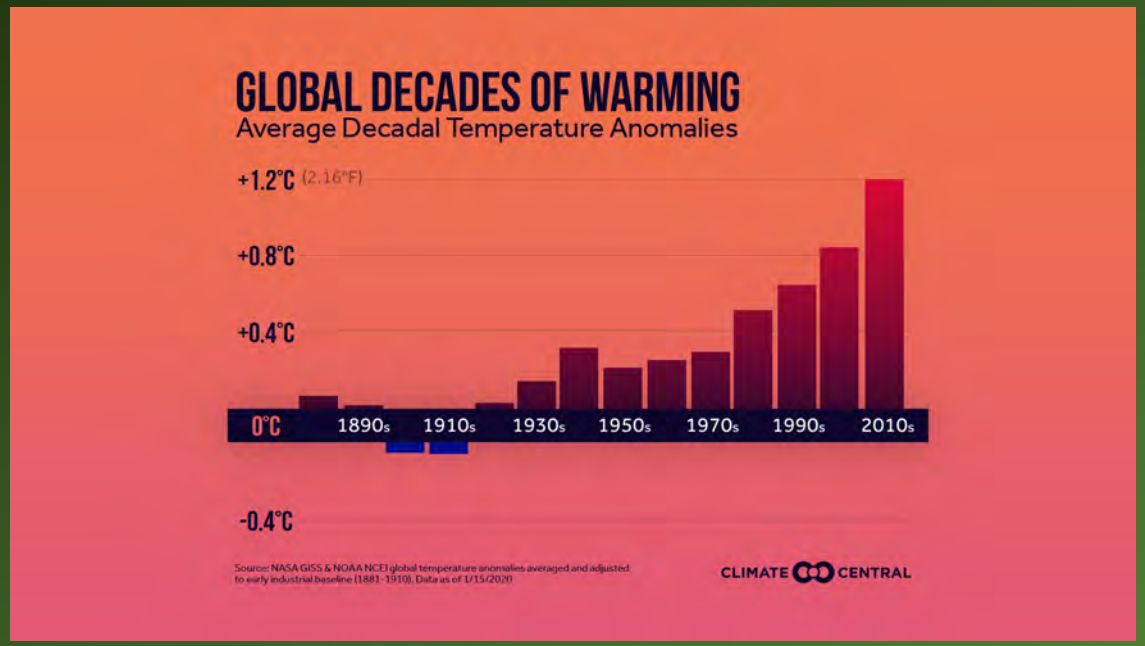


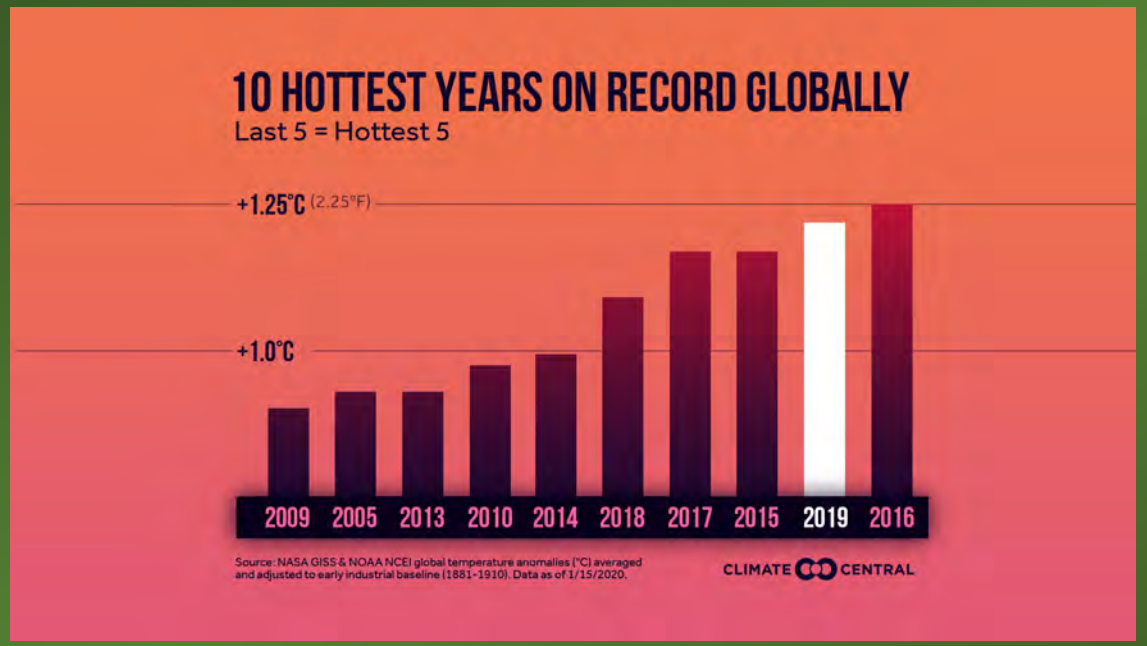
Double Whammy of Climate Change



NOAA , NCEI

While nature can exist without us,
We cannot exist without nature





https://www.climatecentral.org

Parris Climate Agreement has agreed to limit

A Global temperature to 2.2 degree Celsius

B Global temperature to 1.5 degree Celsius

C Ozone level to 70 ppb

D Ambient PM-2.5 concentration to 60 ug/mm^3

Air Pollution: A Sword that Cuts Both Ways

PM 2.5

Asthma, COPD, ARDS

Heart Failure, Angina

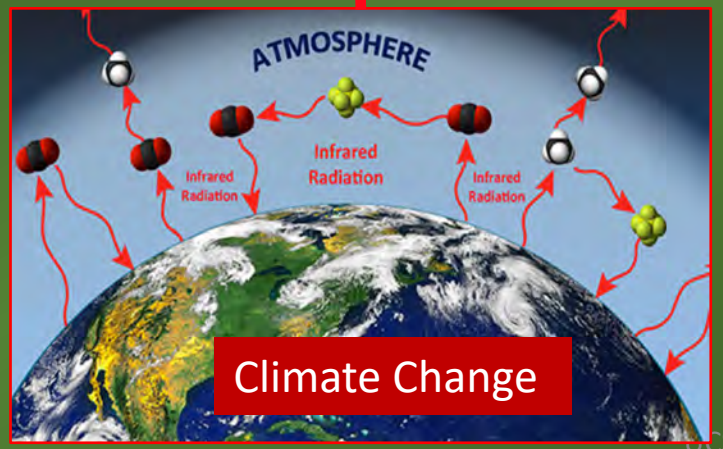
Dementia, Stroke

Emerging Infections

Heated Related illness

O3

O3

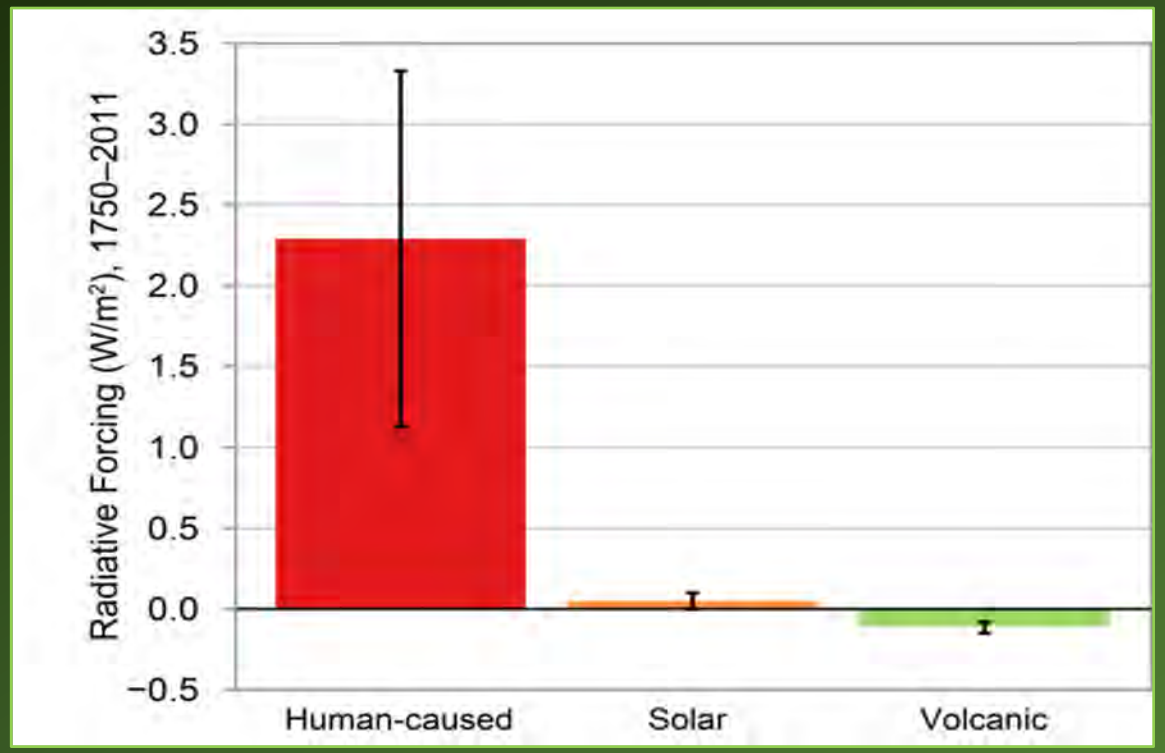


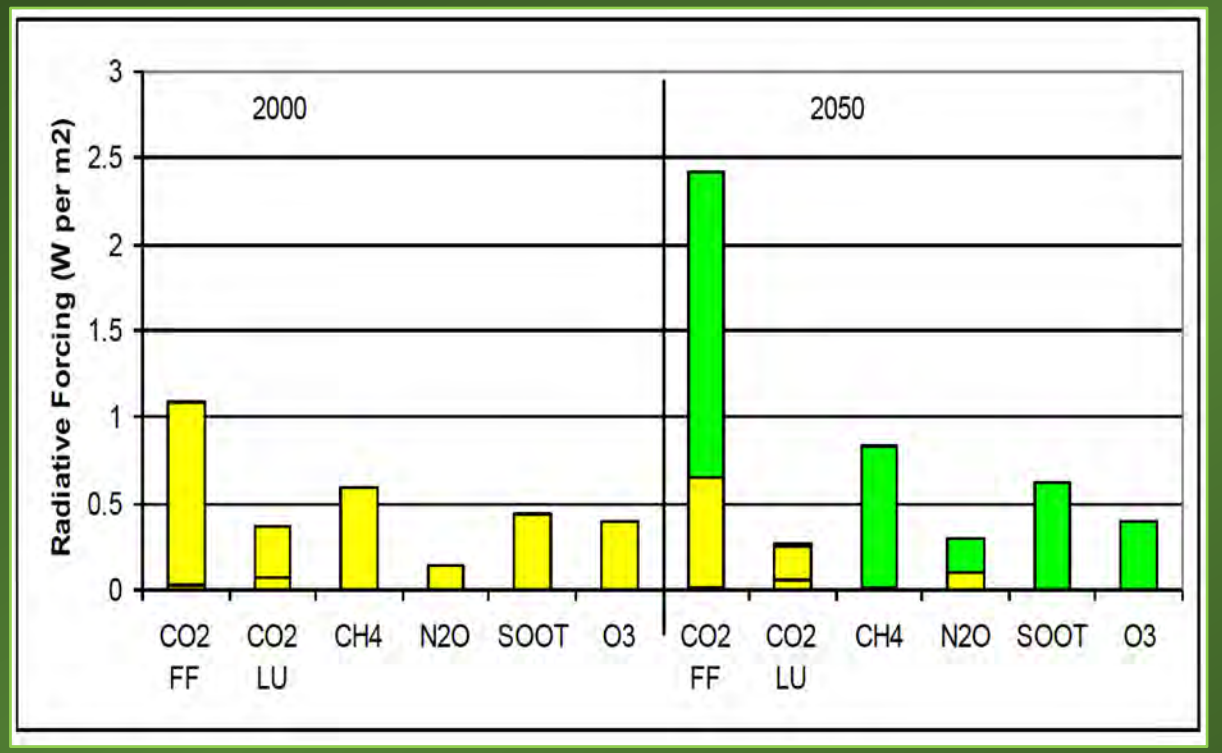
Climate Change

Air Pollution Kills and Drives the Climate Change

- **Global population-weighted fine particulate matter ($PM_{2.5}$) exposure has increased by 11.2% since 1990**
- **about 71% of the 2971 cities in the WHO database exceed guideline annual $PM_{2.5}$ exposure.**
- **WHO has estimated 3.5 million persons/year mortality from outdoor air pollution**
- **Similar number from biomass cookstoves indoor pollution.**

Industrialization has Caused Increase in Radiative Forcing

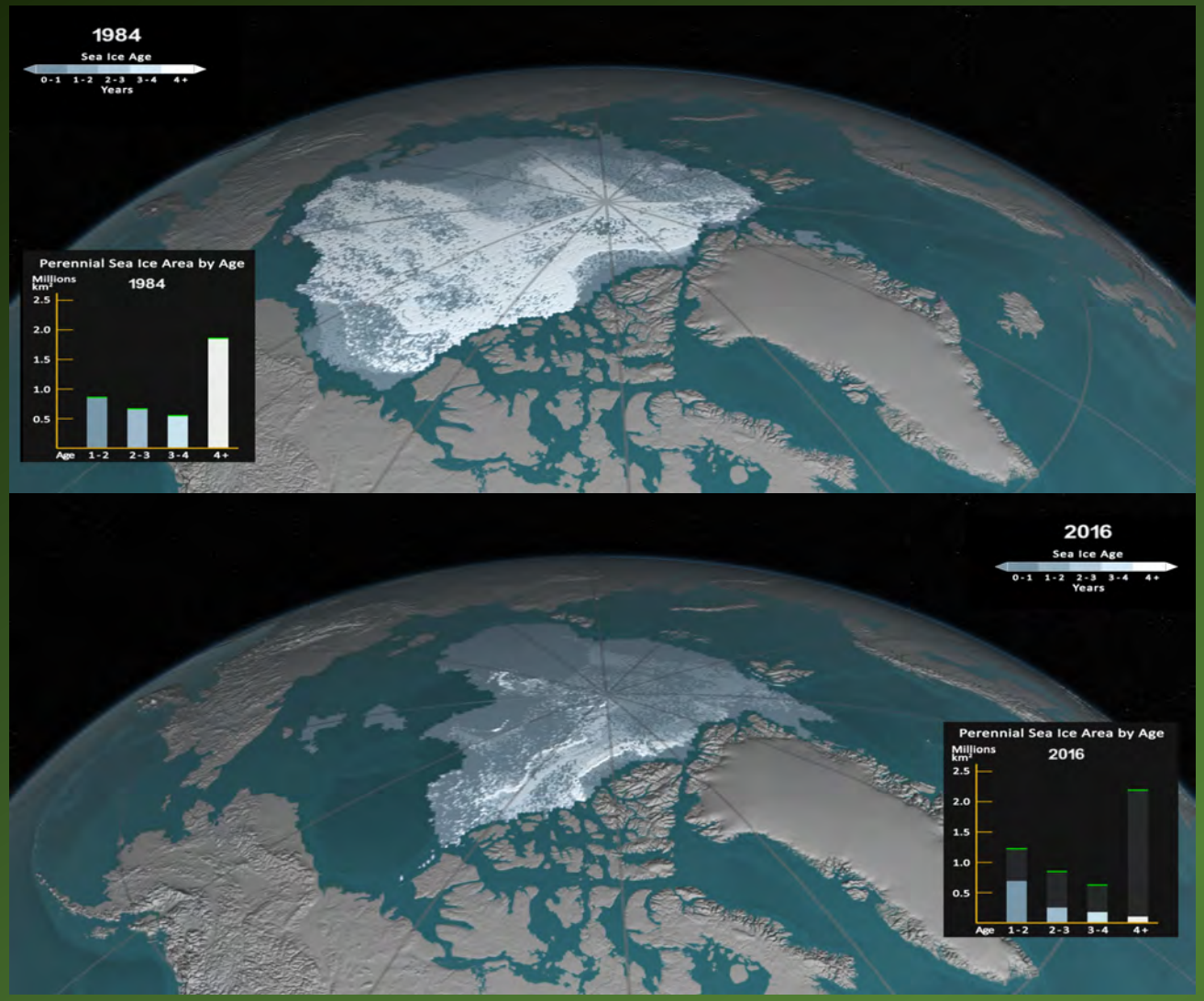


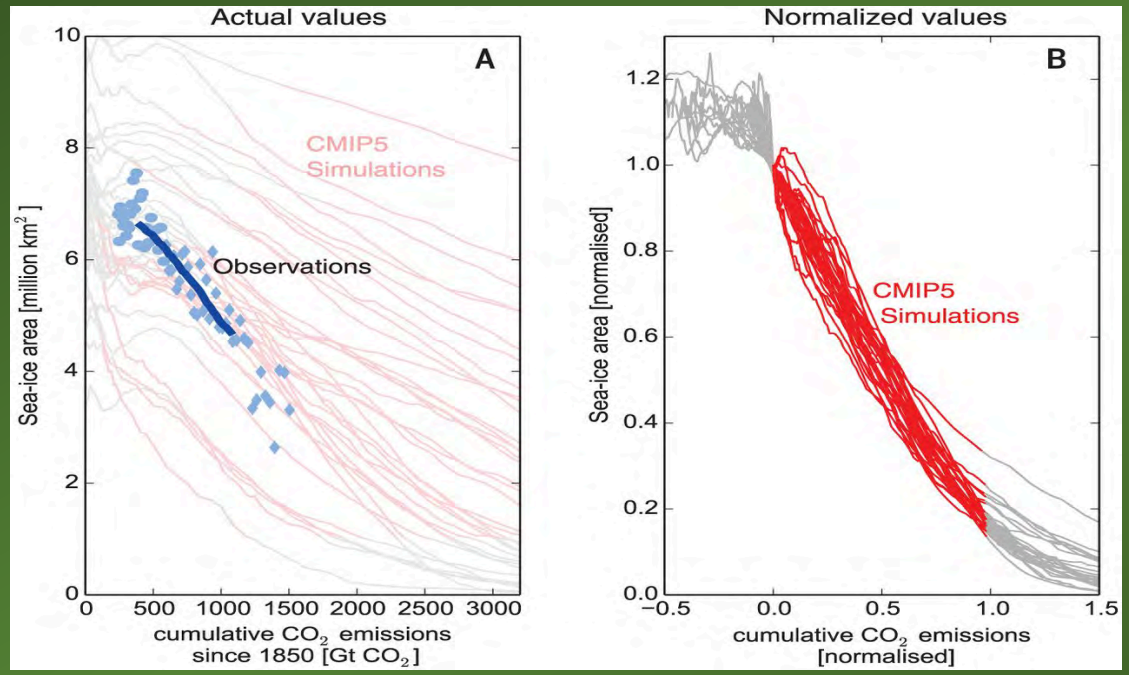


Moore FC, Sustainability 2009

Consequences of Global Warming

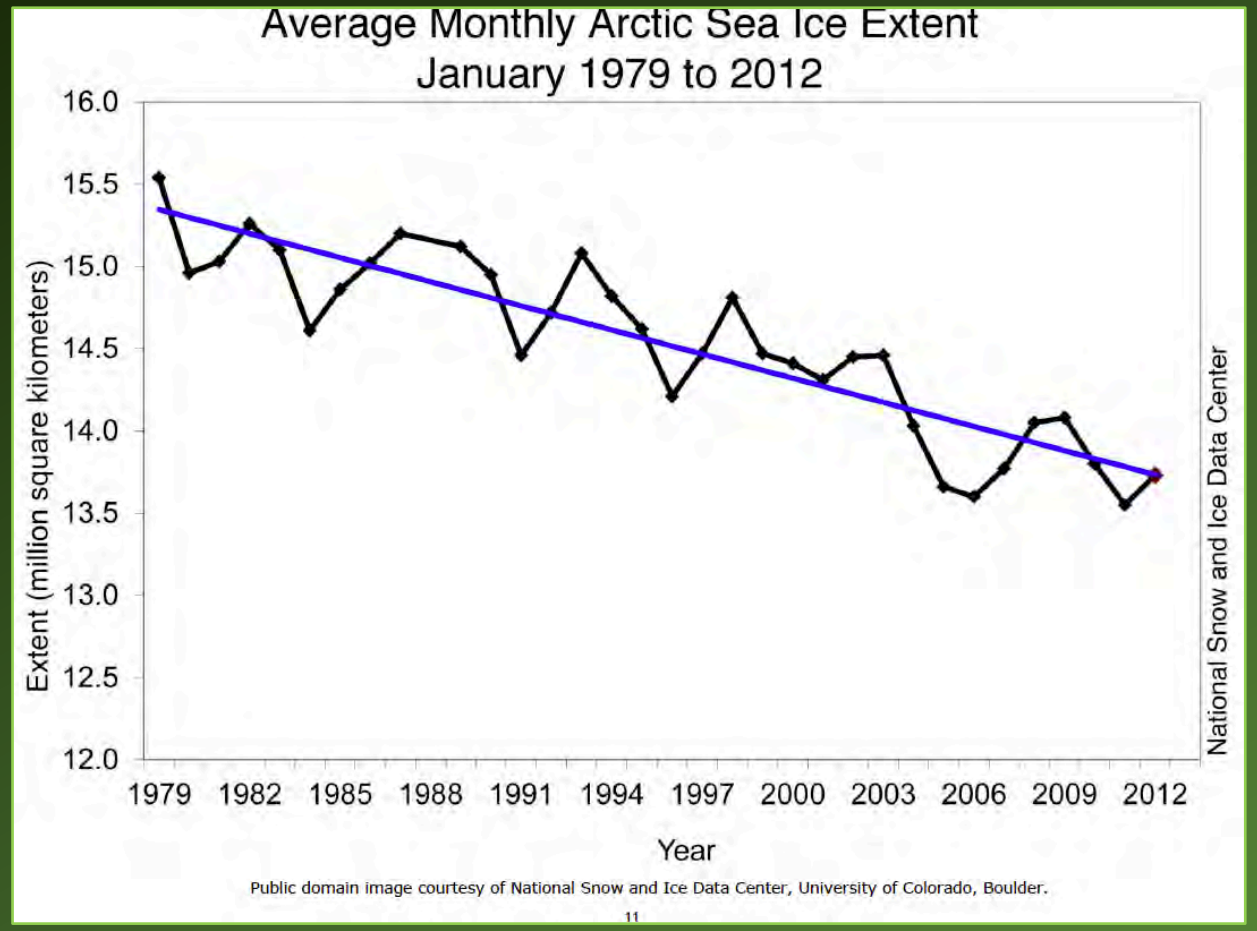
The Mighty Meltdown: Loss of Multi-year "Old" Arctic Sea Ice from 1984 to 2016

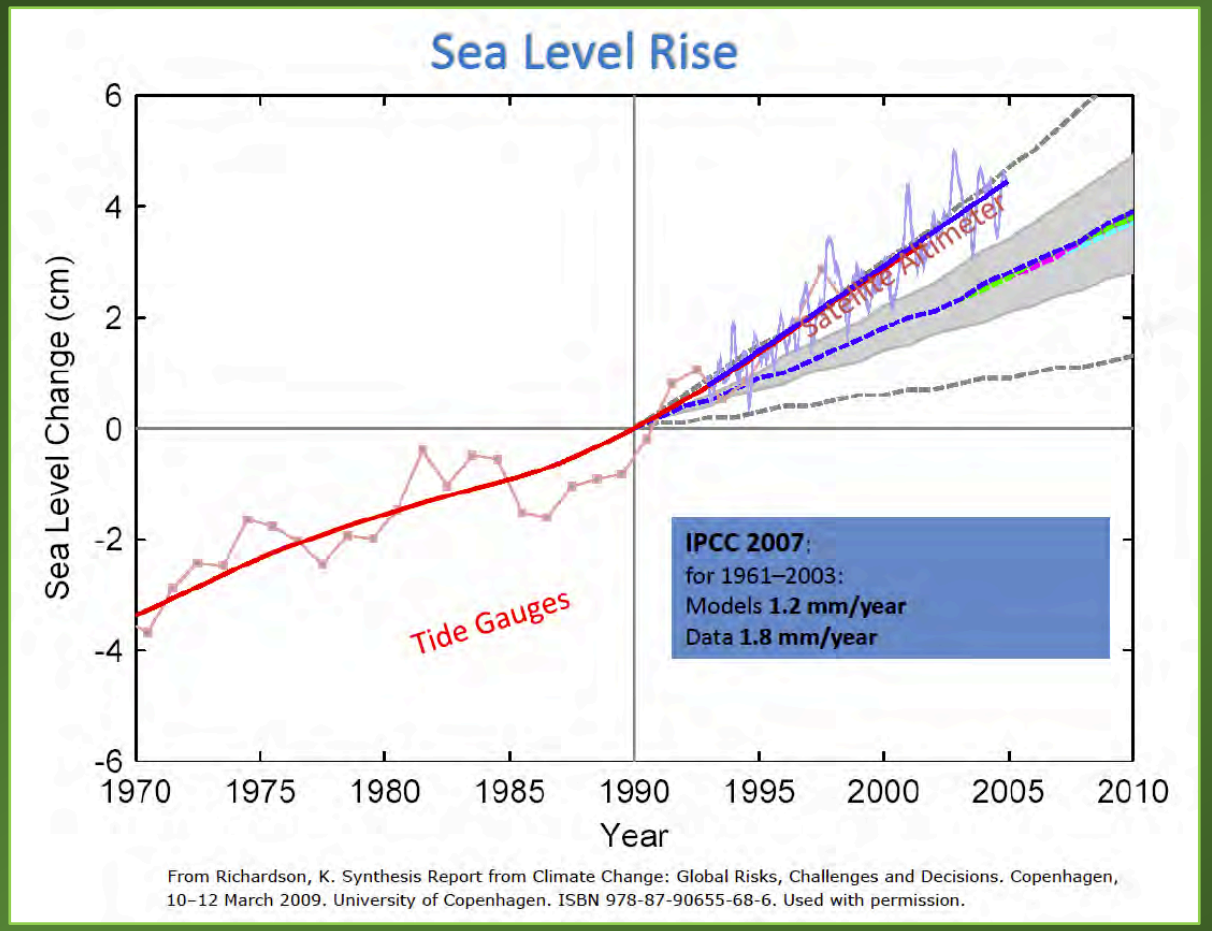




NOAA

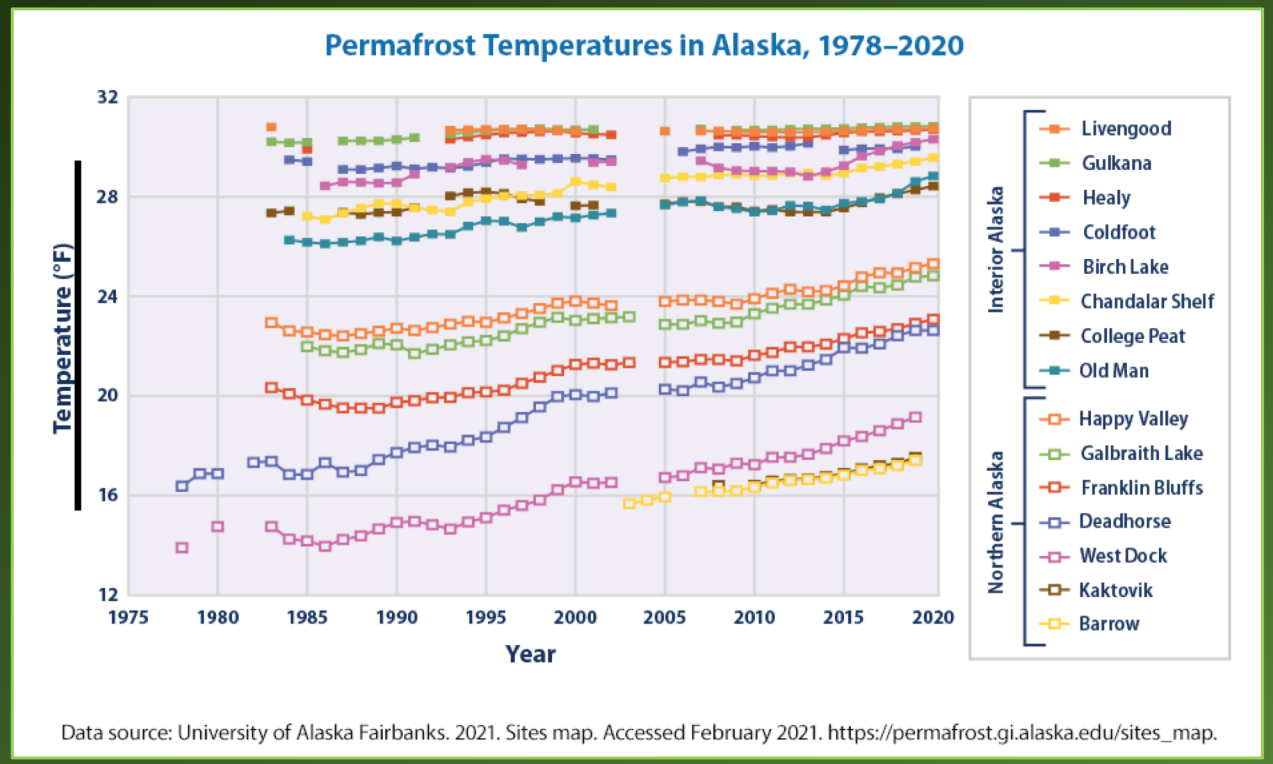
Artic Ice Melt & Sea Level Rise



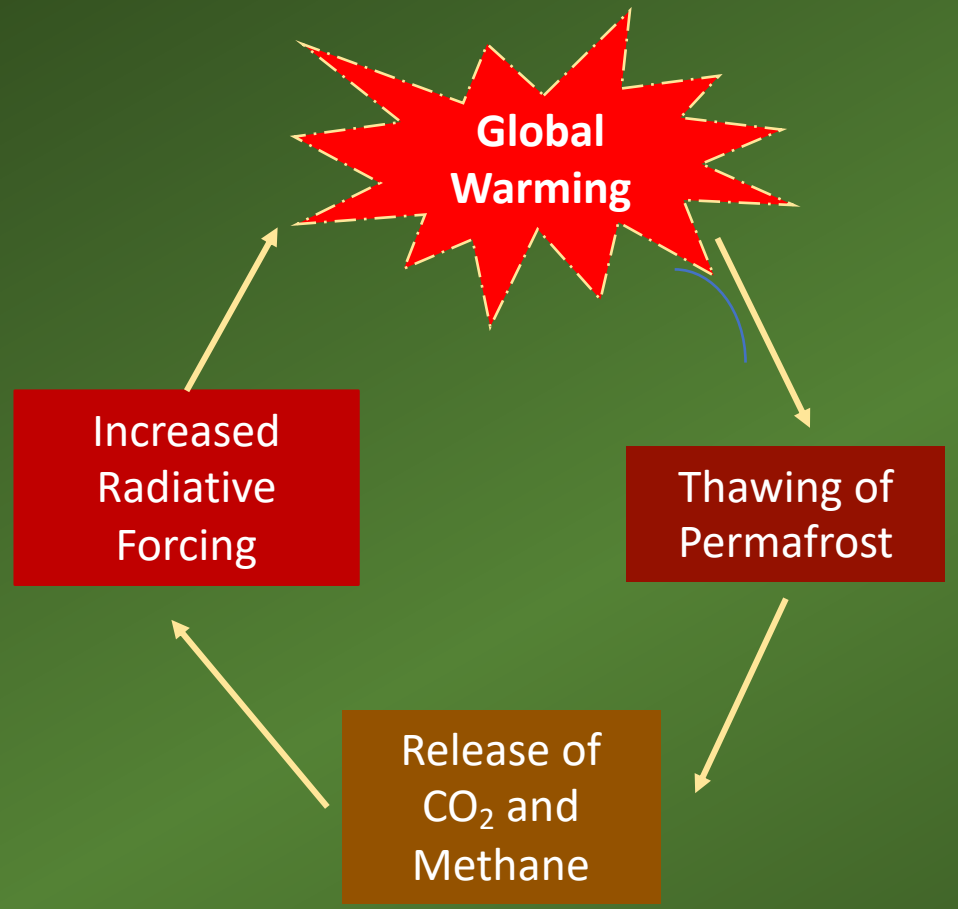


NOAA

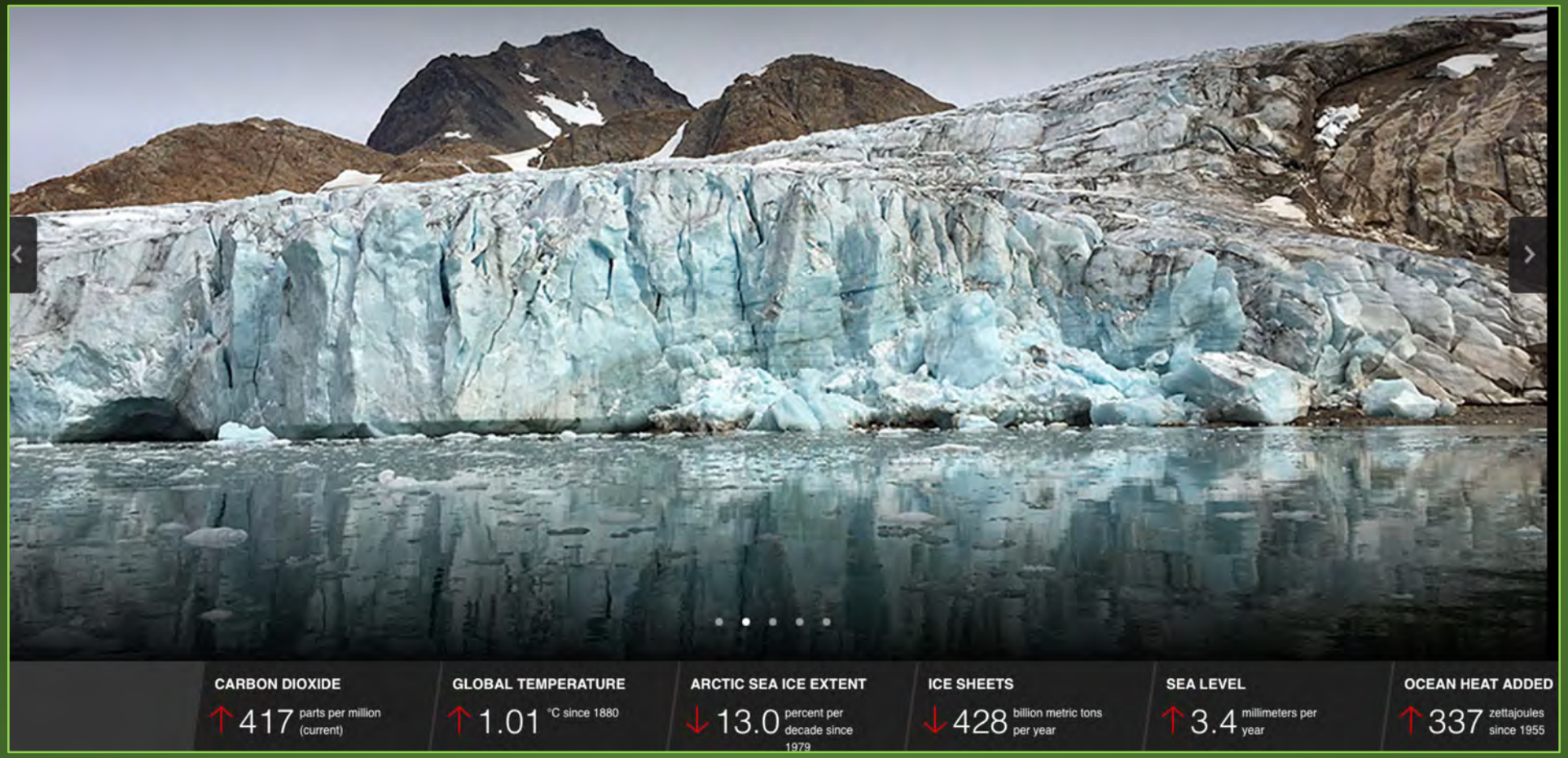
Beginning of a Deadly Vicious Cycle



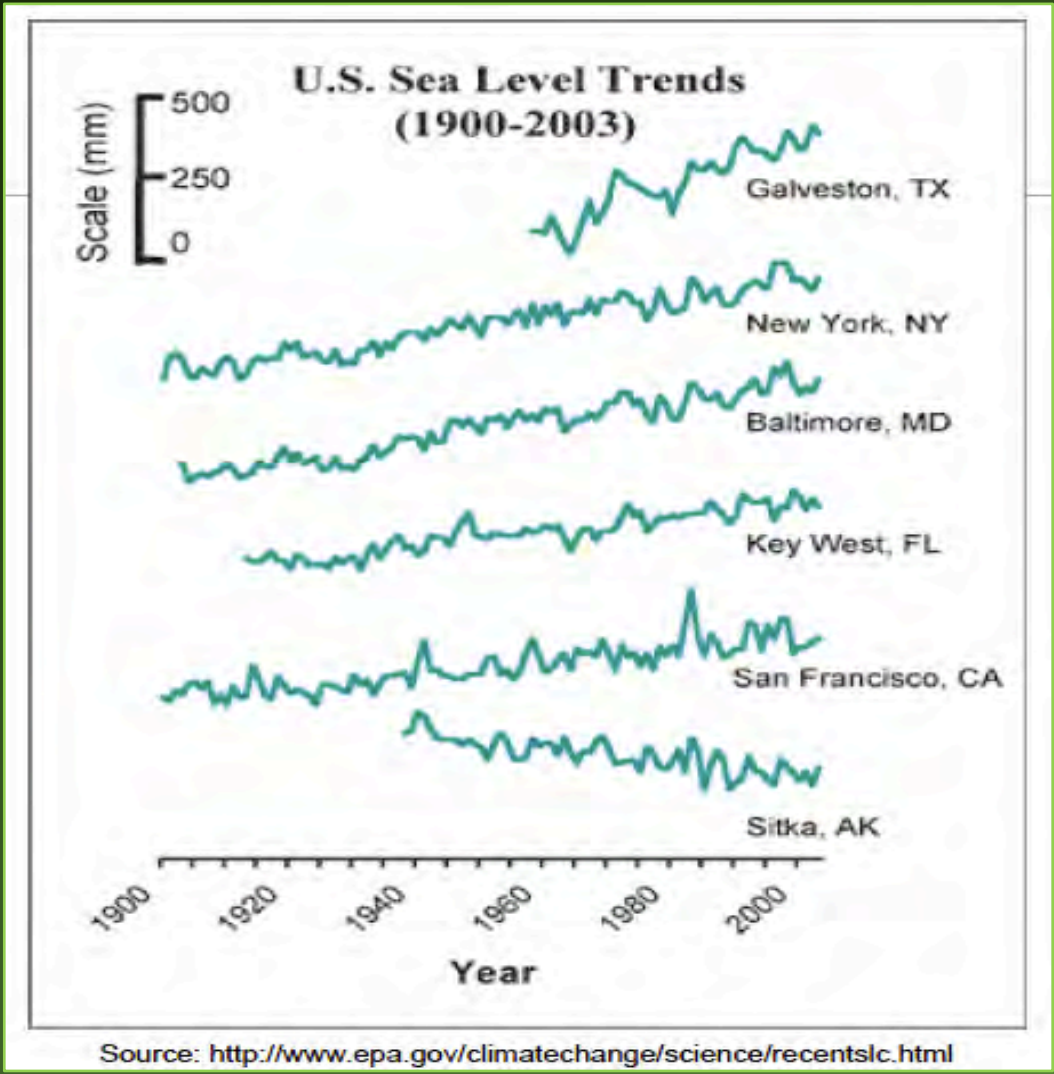
Data source: University of Alaska Fairbanks. 2021. Sites map. Accessed February 2021. https://permafrost.gi.alaska.edu/sites_map.



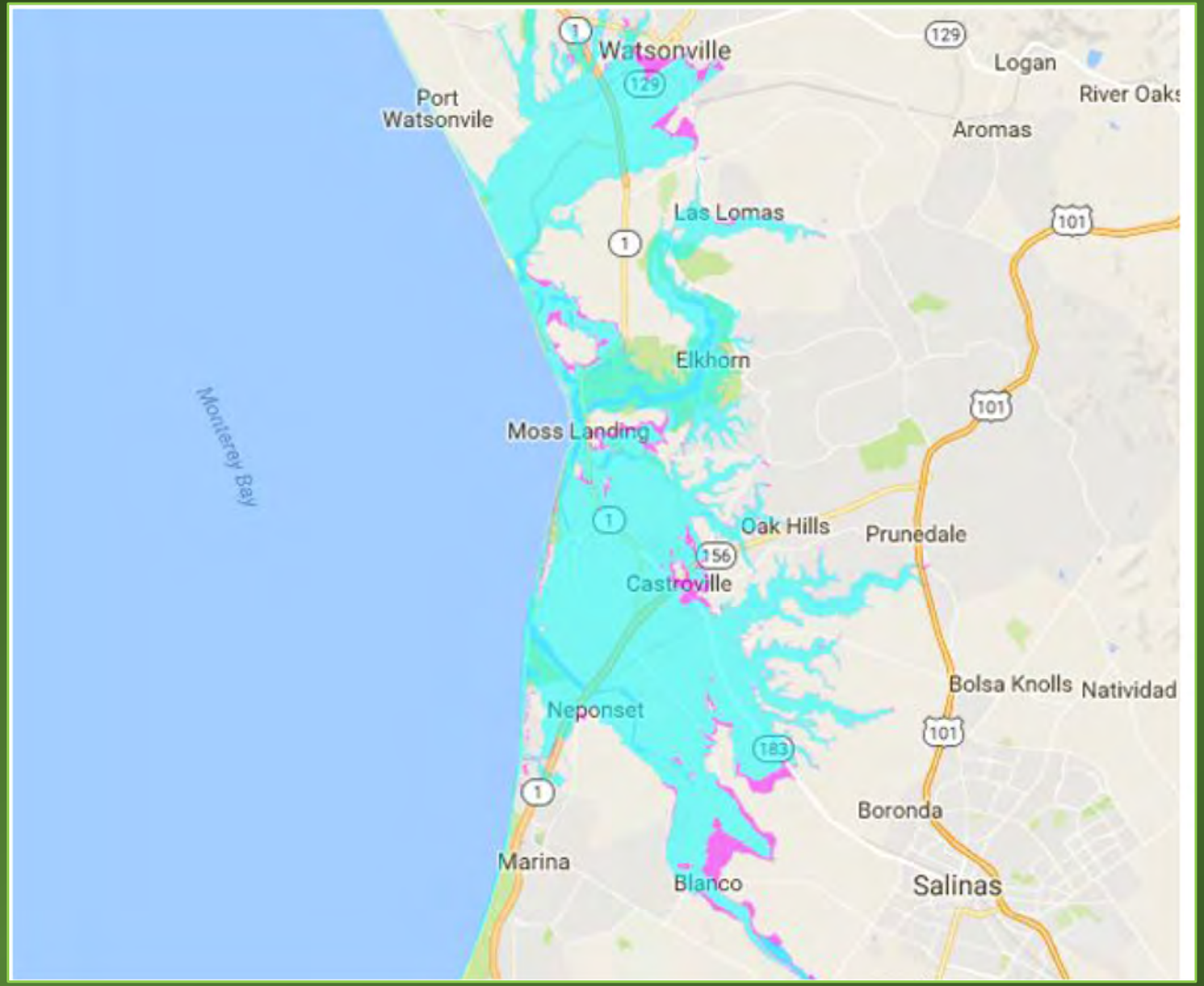
Vital Signs of Planet are No Good: NASA



Climate Change: We have a lot to Lose including Dungeness Crab



Source: http://www.epa.gov/climatechange/science/recentslc.html

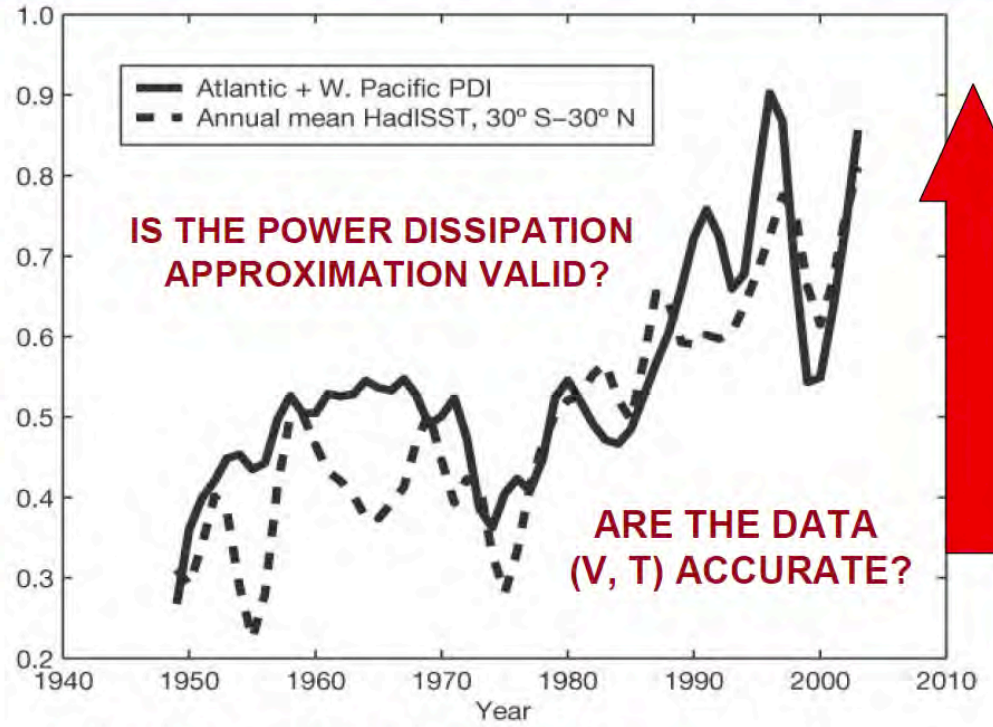


MIT Open Course/Pacific Institute

Climate Change & Hurricanes

HURRICANES:
INCREASING DESTRUCTIVENESS OVER THE PAST 30 YEARS?

Power Dissipation Index (PDI) = $\int_0^T V_{max}^3 \, dt$ (a measure of storm destruction)

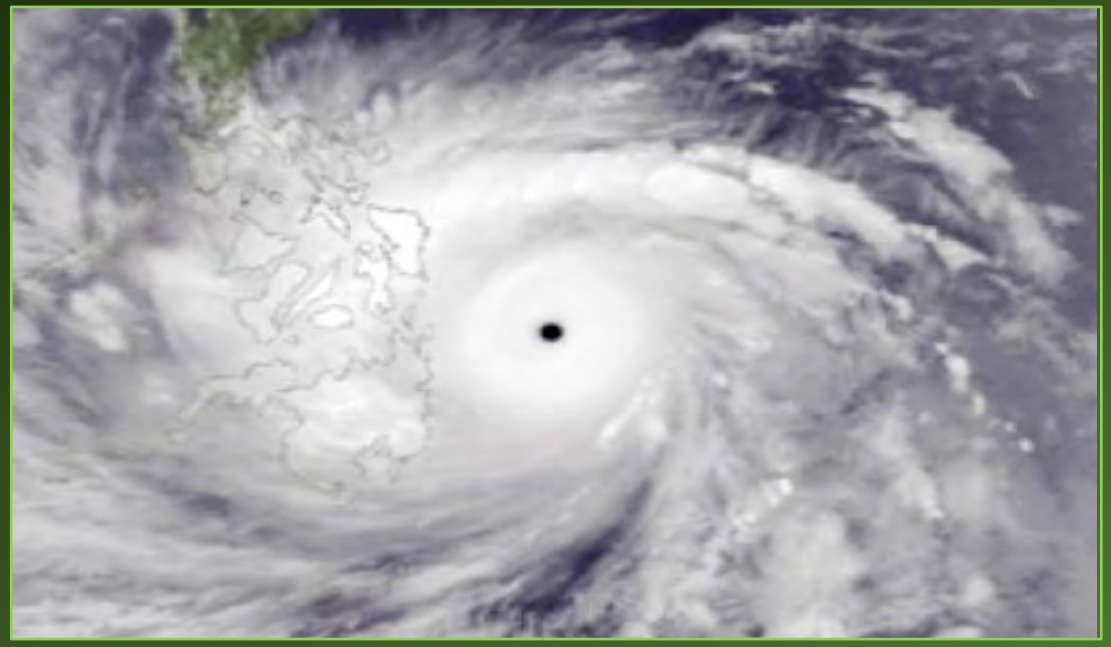


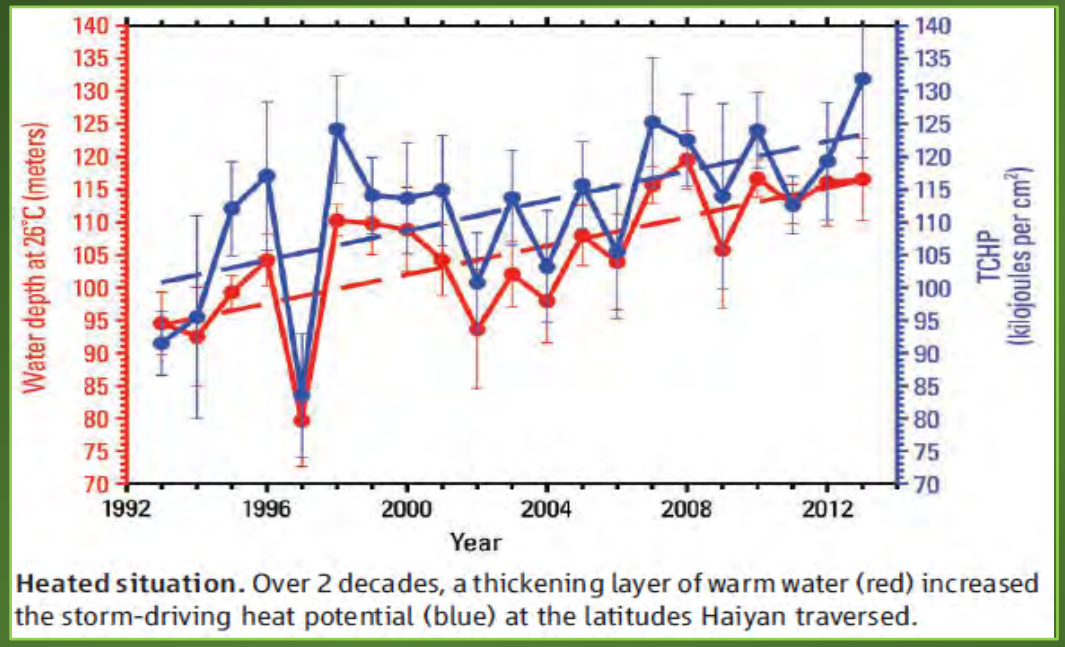
Courtesy of Kerry Emanuel. Used with permission.

SOURCE: Emanuel, K., *Nature*, vol. 436, 4 August 2005

Emanuel K, Nature 2005

Tropical Cyclone Heat Potential has Increased by 20%





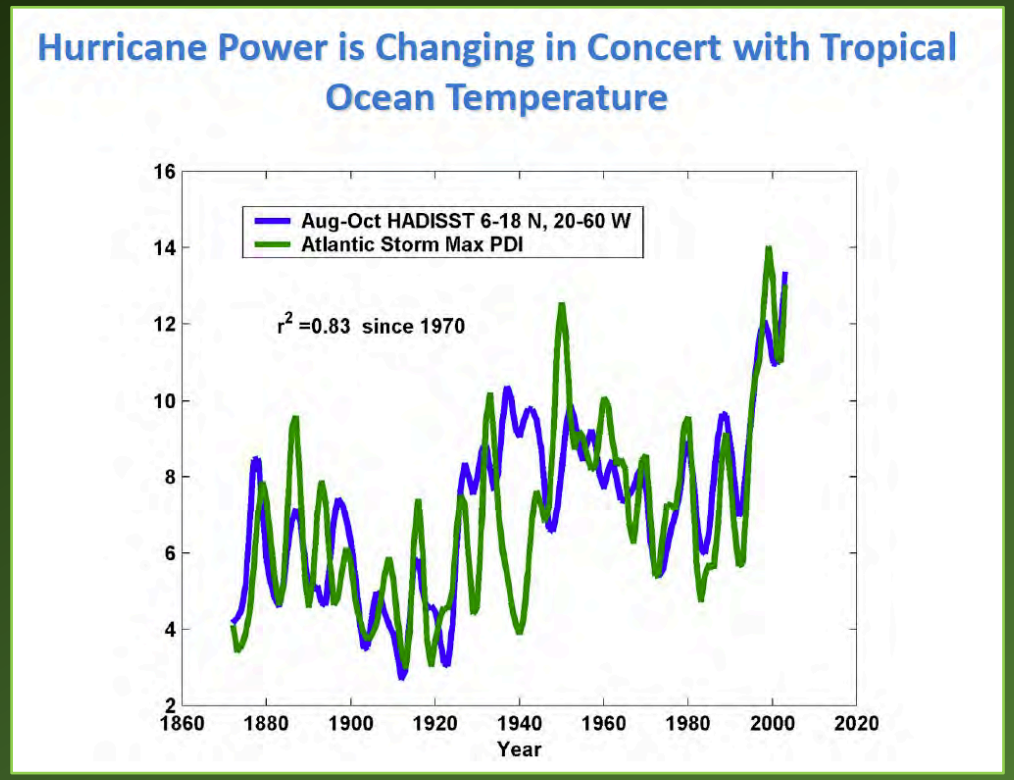
Heated situation. Over 2 decades, a thickening layer of warm water (red) increased the storm-driving heat potential (blue) at the latitudes Haiyan traversed.

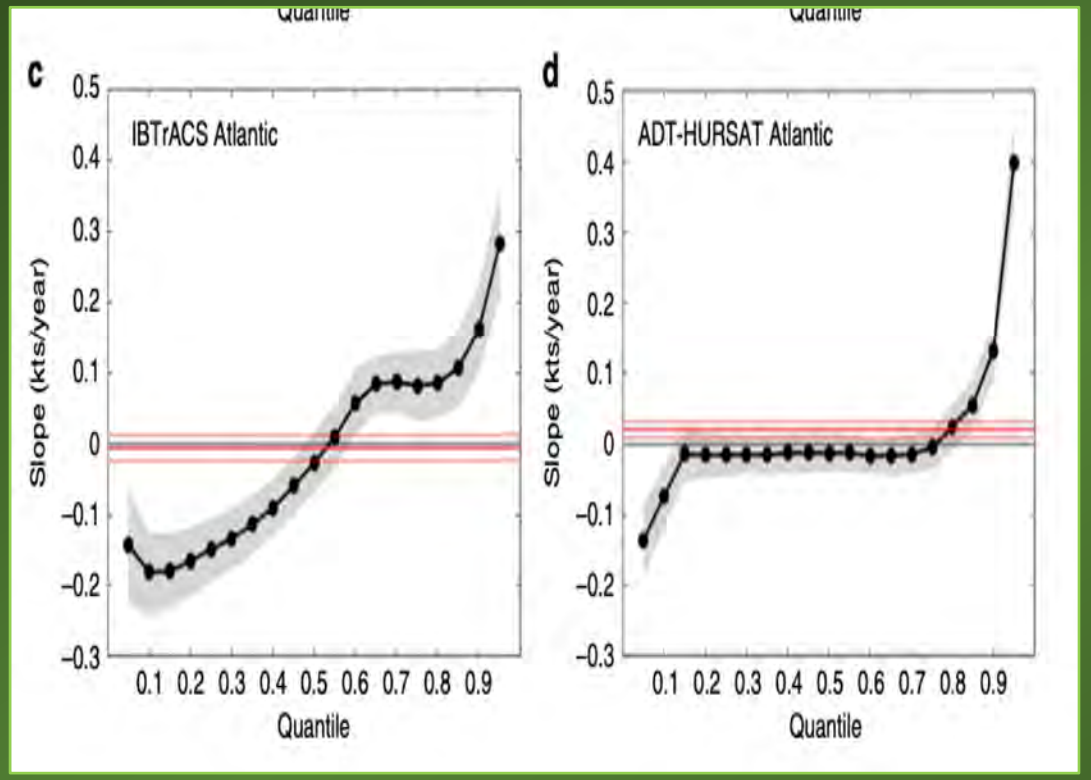
Typhoon Haiyan 2013

Wind Speed: 196 mph

Fatality 6340, Damage: 2.98 billion

Hurricane Power , Frequency & Rapid Intensification





Rapid Intensification Index 1982-2009

NOAA

Kiren Bhatia, Nature Communications 2019

US Tornadoes Frequency 1950 to 2006

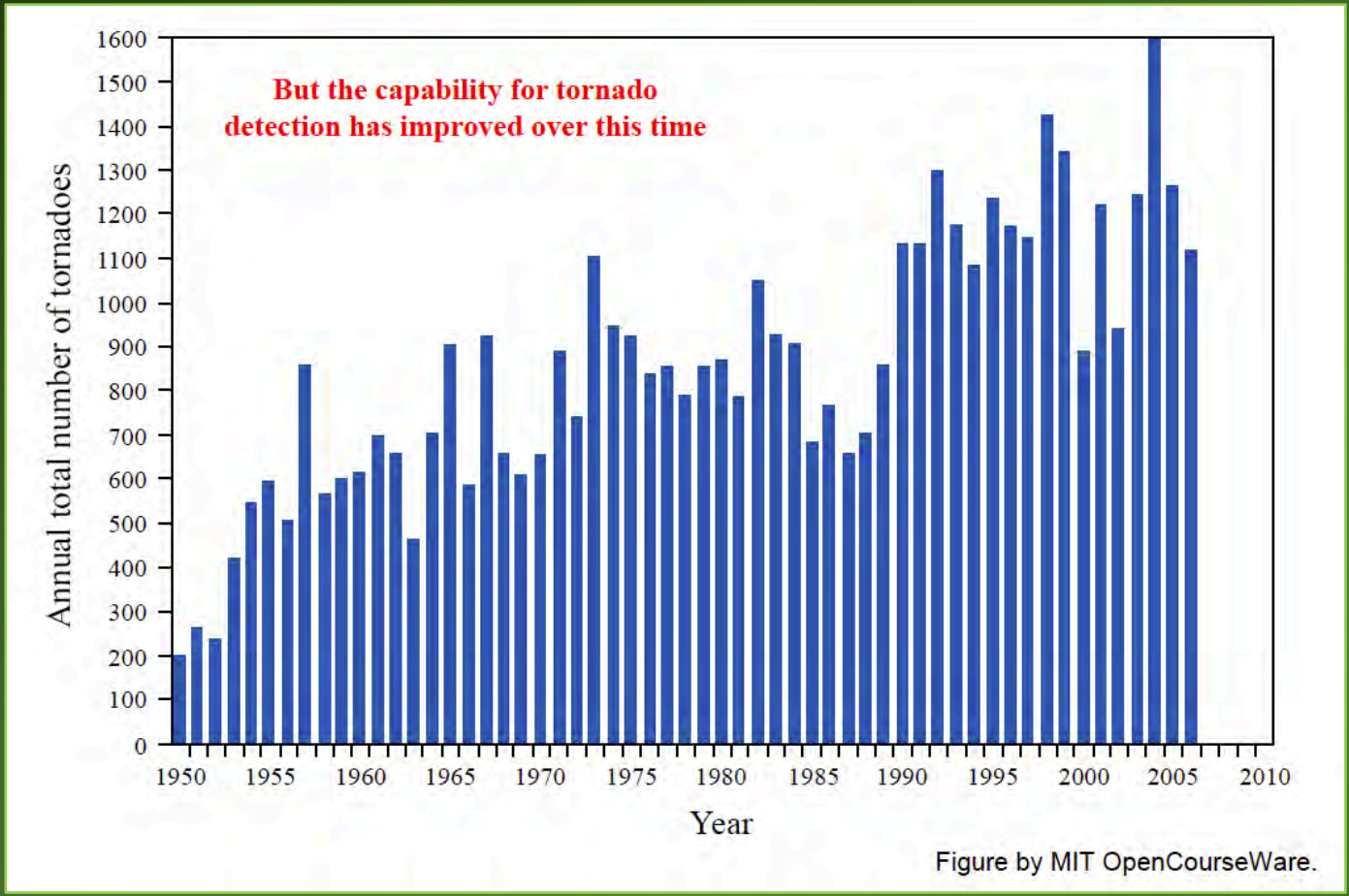
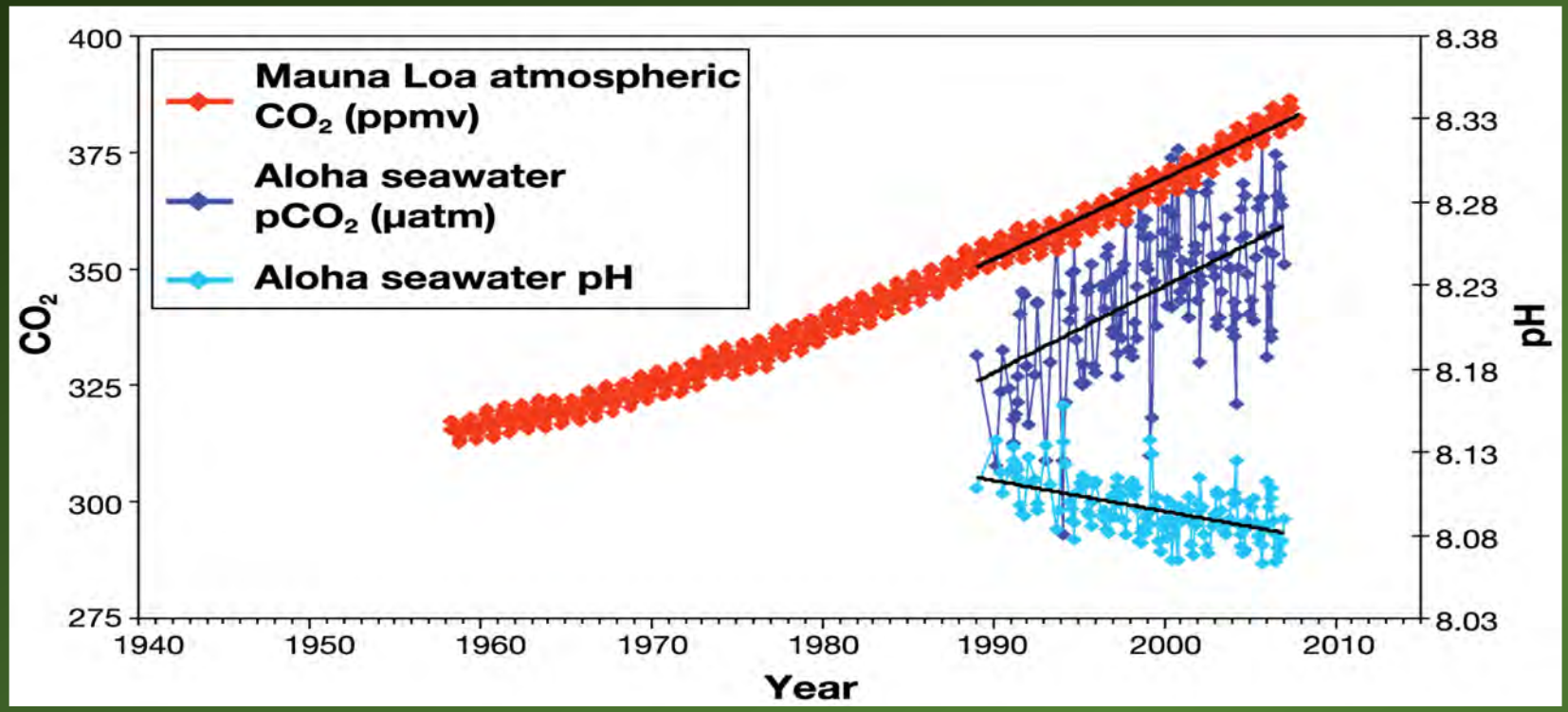


Figure by MIT OpenCourseWare.

Atmospheric CO_2 and Ocean pH



The link is that dissolved CO_2 forms weak carbonic acid ($H_2O + CO_2 \rightarrow H_2CO_3$), lowering the pH

Years of Living Dangerously
National Geographic

These staghorn corals off the coast of Guam appeared bleached in October 2017. (David Burdick / AP)

Coral reefs around the globe will completely die off and be replaced by slime by 2045.

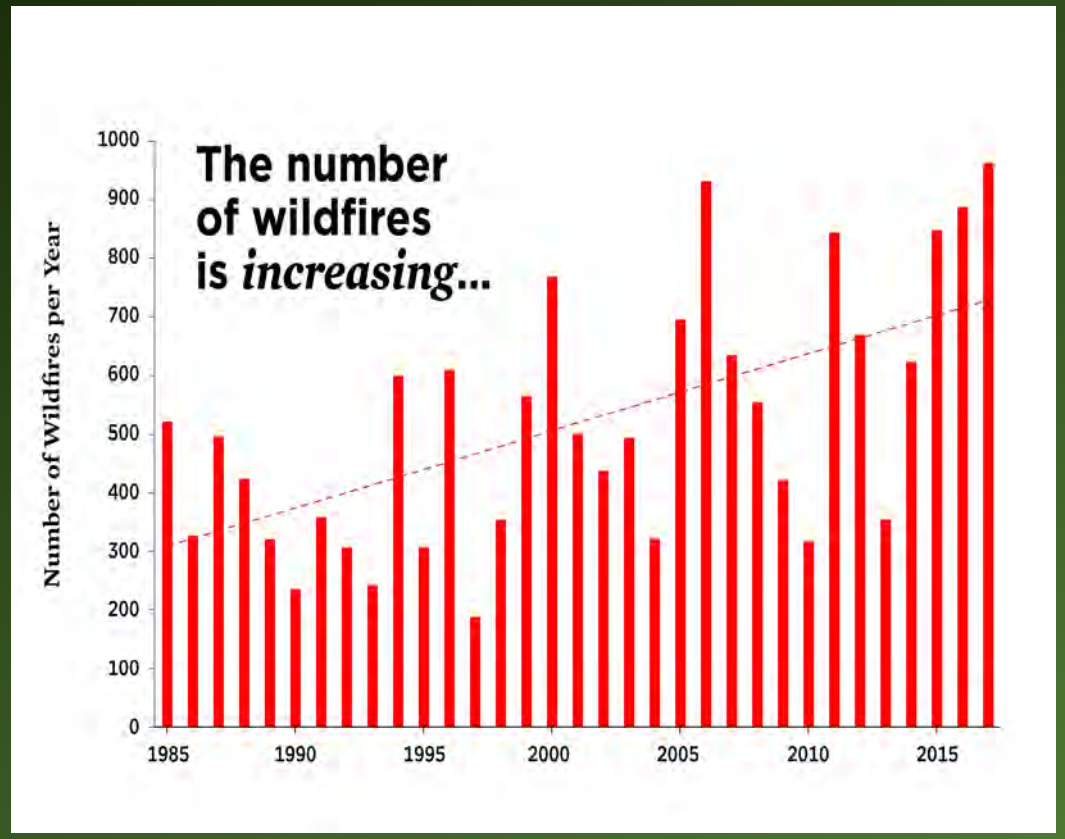
Half of the Great Barrier Reef had died off during the heat of 2016.

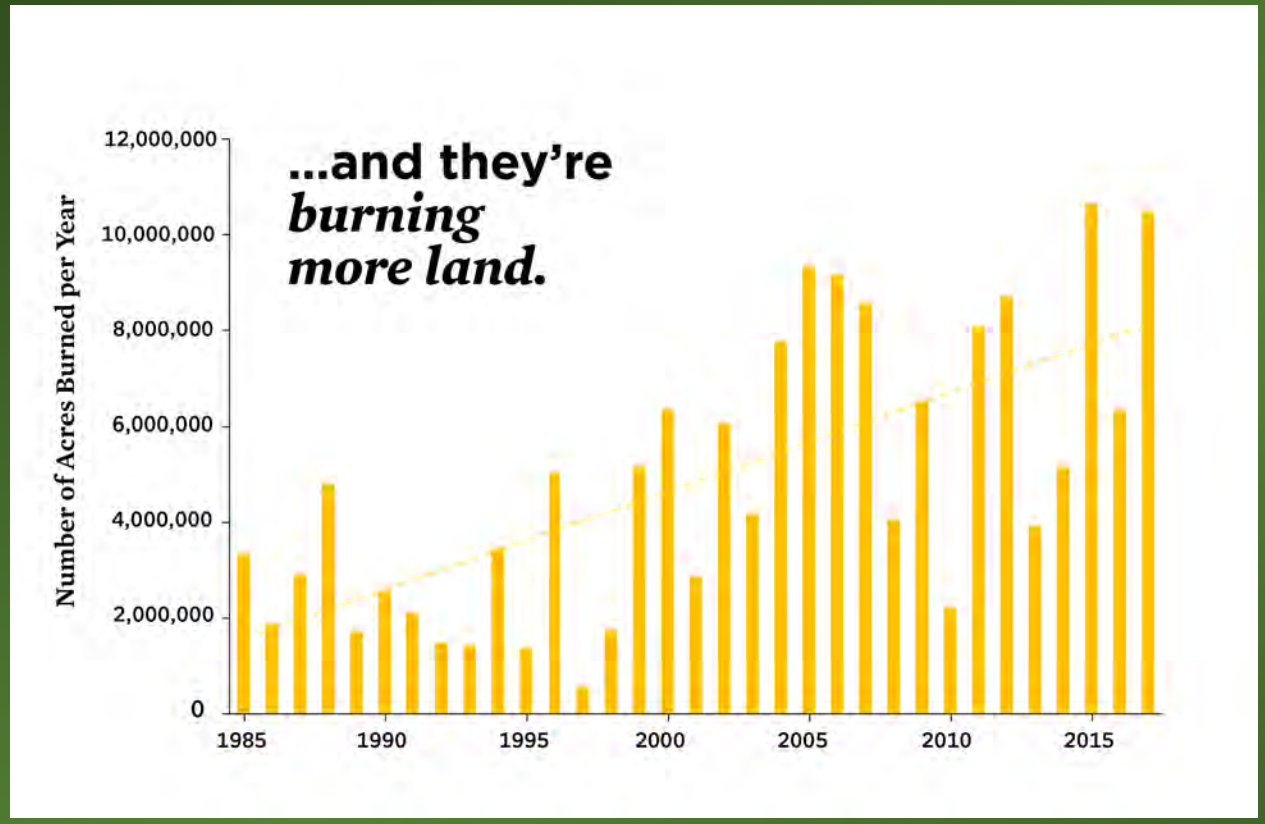
California Under Siege from Forrest Fires Every Summer-Fall

The planet is on a 'catastrophic' global warming path, UN report shows

By Rachel Ramirez, CNN
Published 1:08 PM EDT, Fri September 17, 2021

Wild Fires Frequency and Acres are Increasing





Climate Change and Vegetations

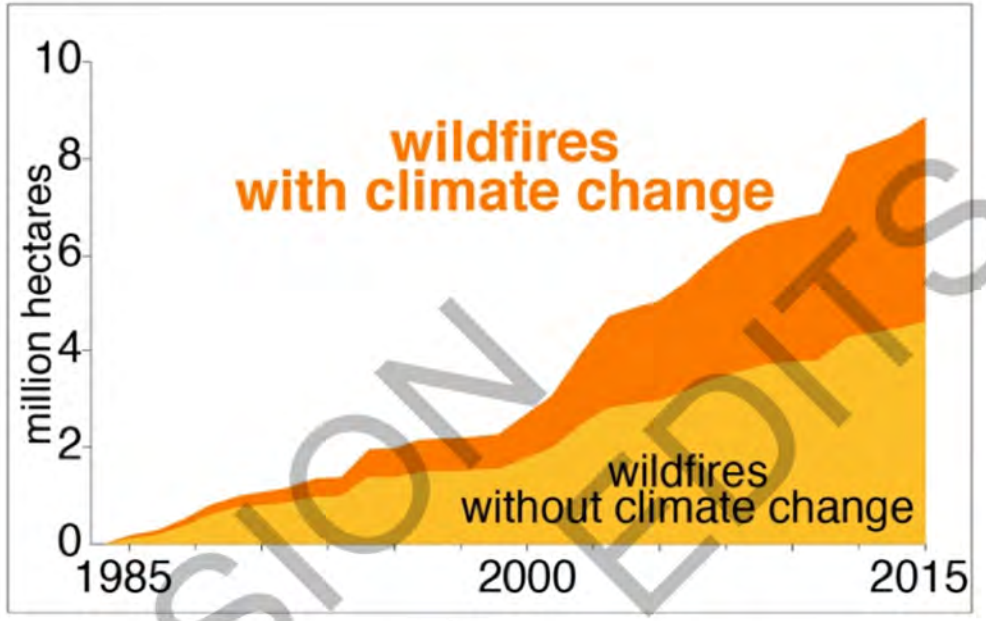
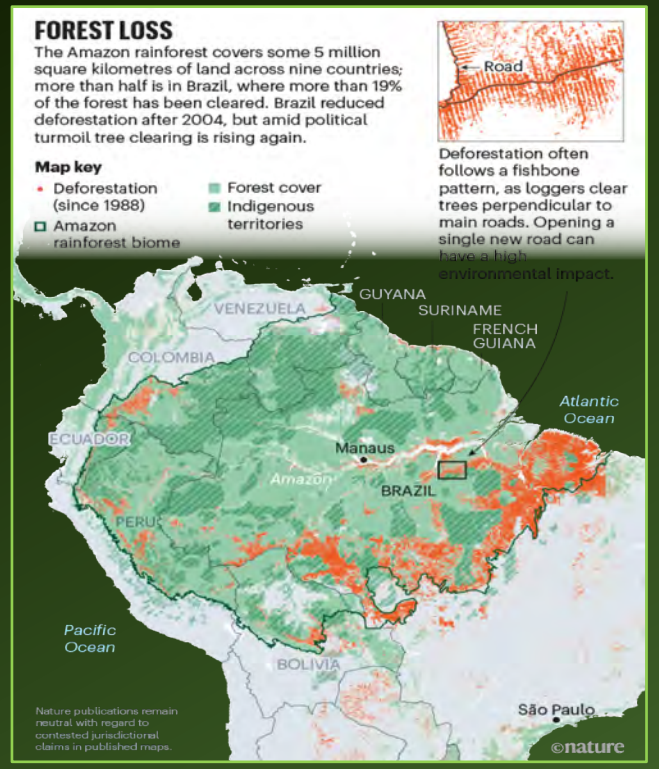


Figure FAQ2.3.1: (a) Springs Fire, May 2, 2013, Thousand Oaks, California, USA (photo by Michael Robinson Chávez, Los Angeles Times). (b) Cumulative area burned by wildfire in the western U.S., with (orange) and without (yellow) the increased heat and aridity of climate change (Abatzoglou and Williams, 2016).

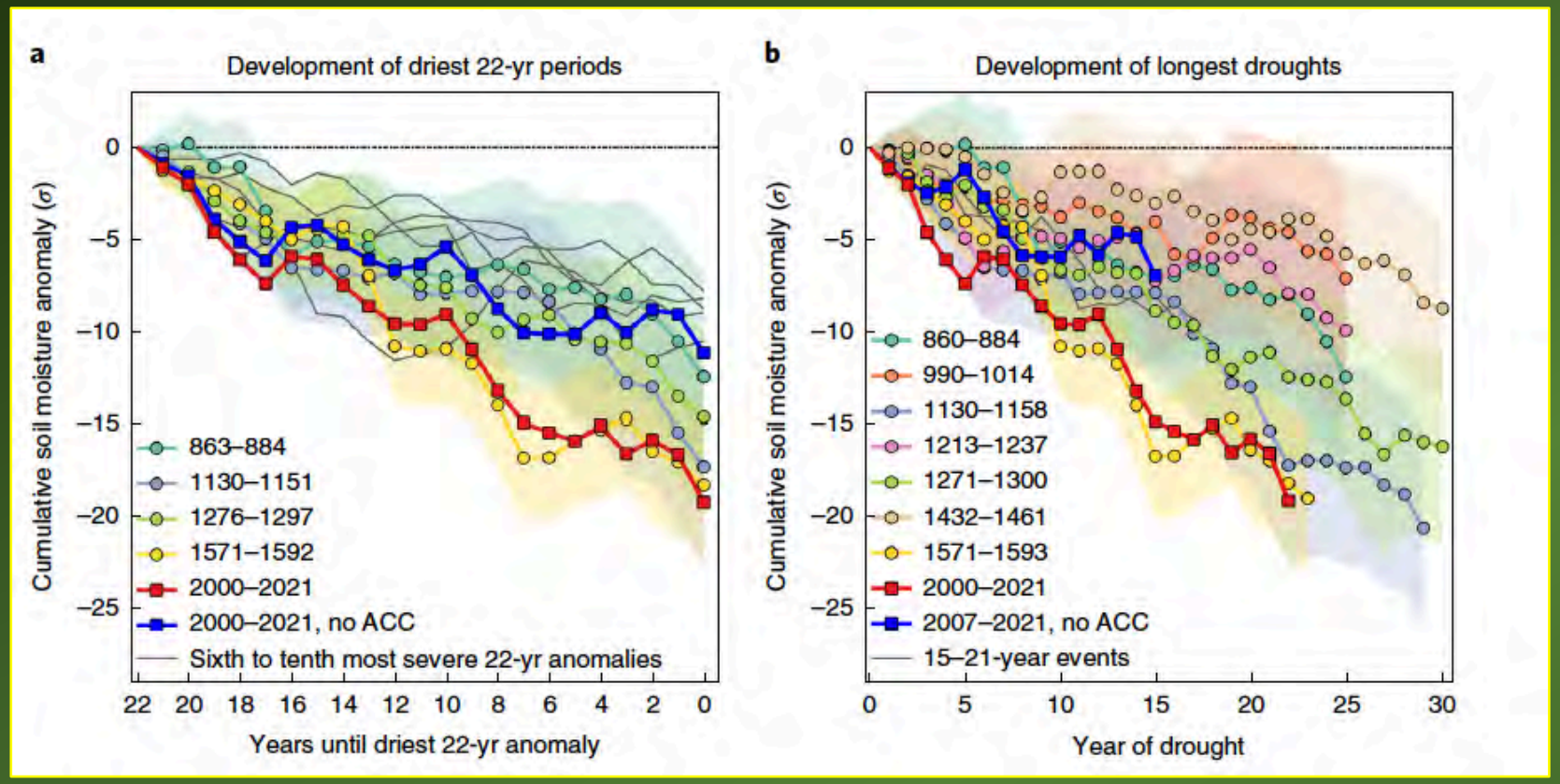
Adding Fuel to Fire



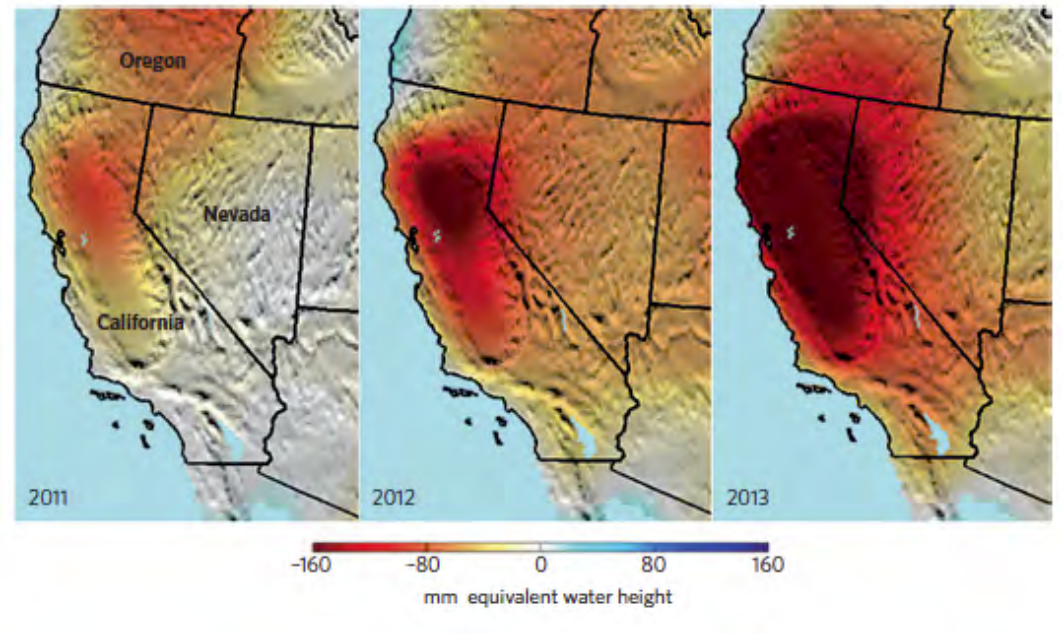
Nitrogen Fixation works best at 25 Celsius

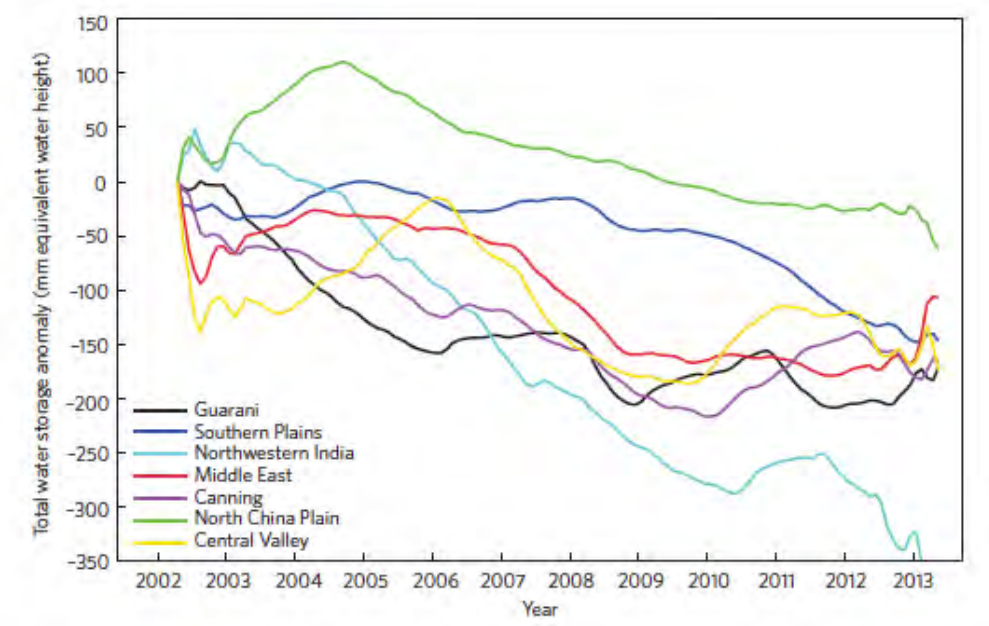
NATURE 2020; 578: 27Feb

Mega Droughts



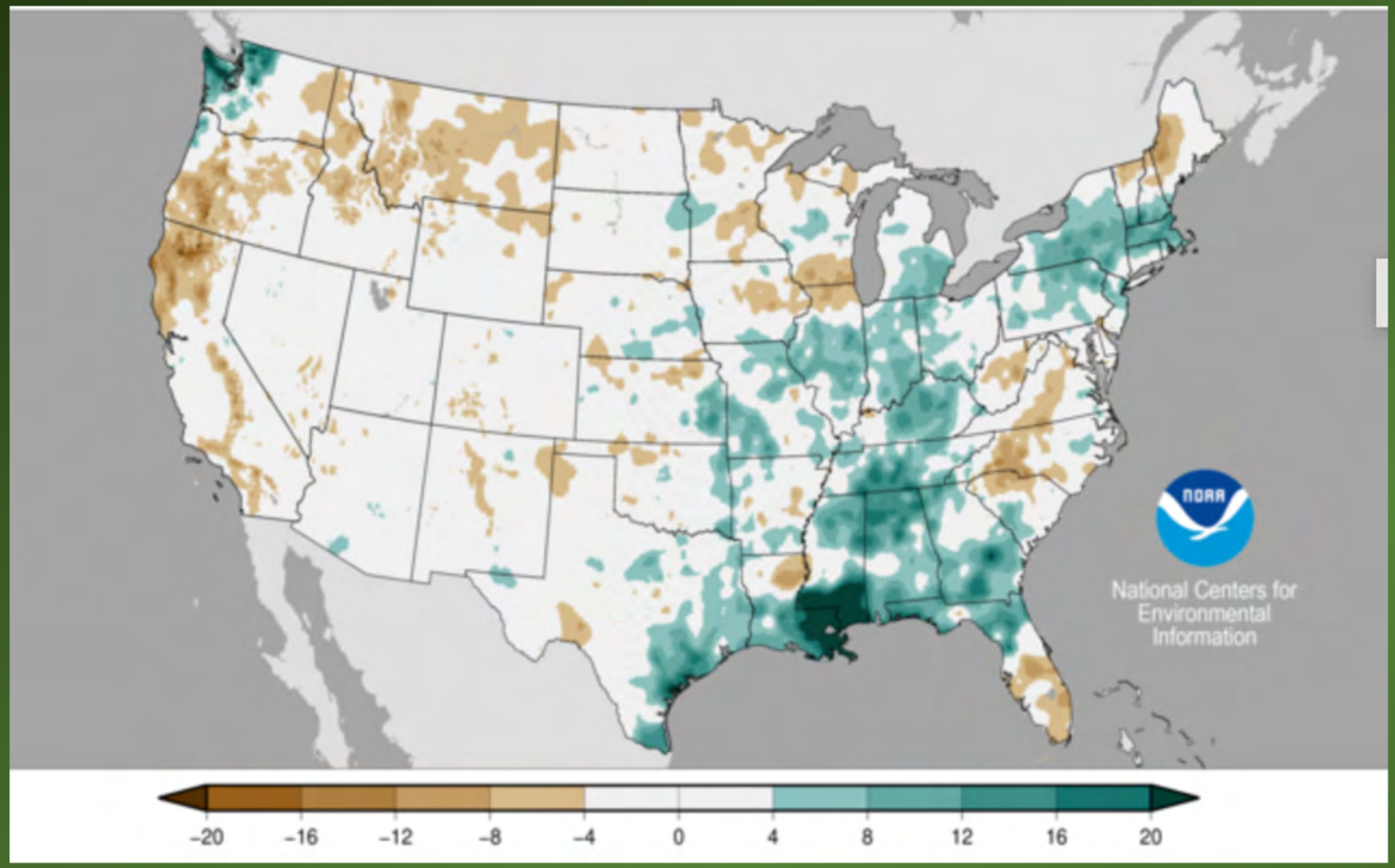
Global Aquafer Depletion



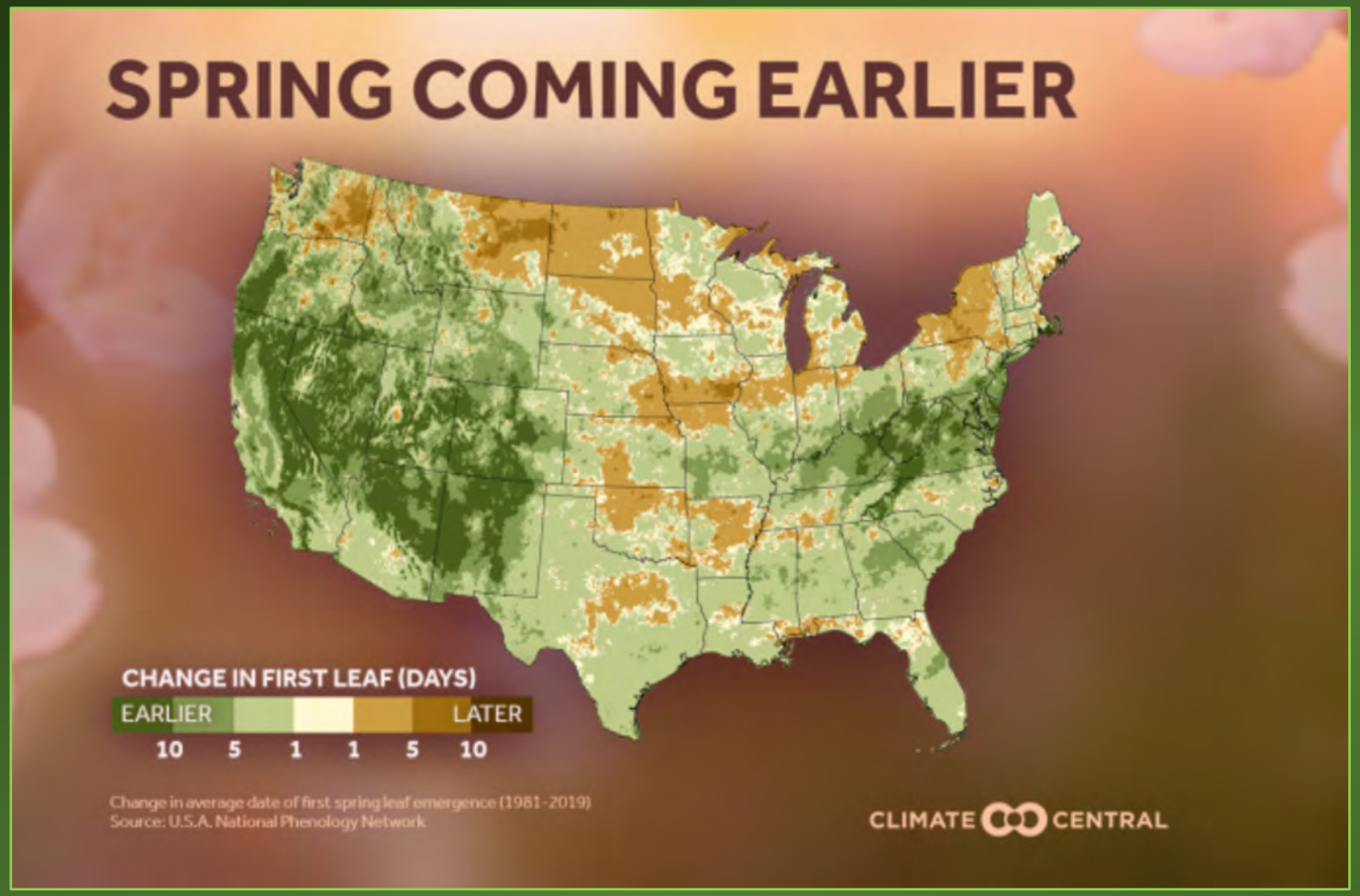


Famiglietti JS, Nature Climate Change 2014
Landerer WL, NASA Jet Propulsion Lab

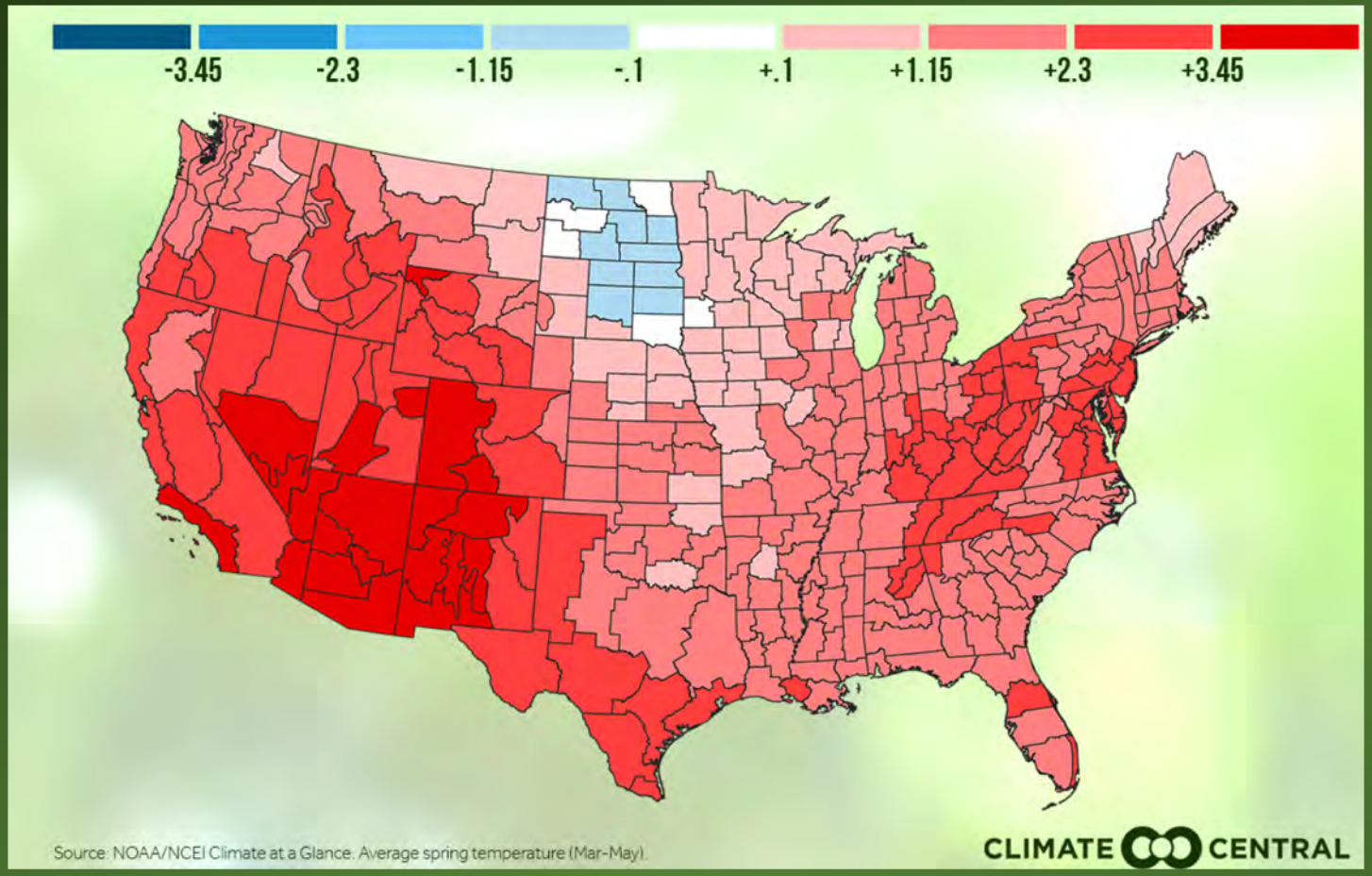
Precipitation Departure from Average Jan-Dec 2021



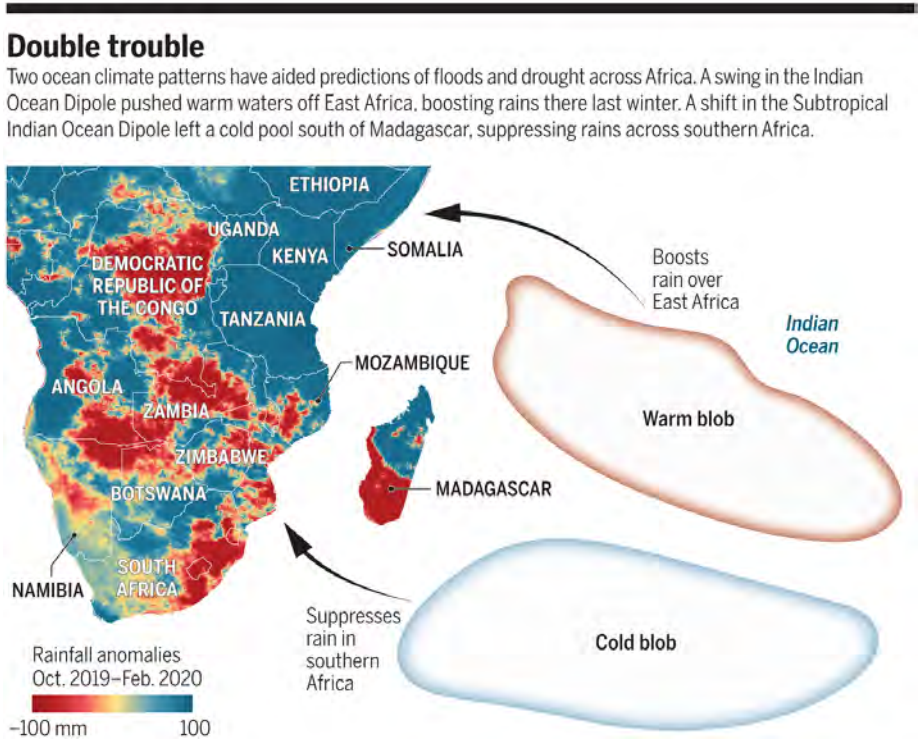
Shorter Winter & Longer Summer



Spring Warming from 1970 to 2021



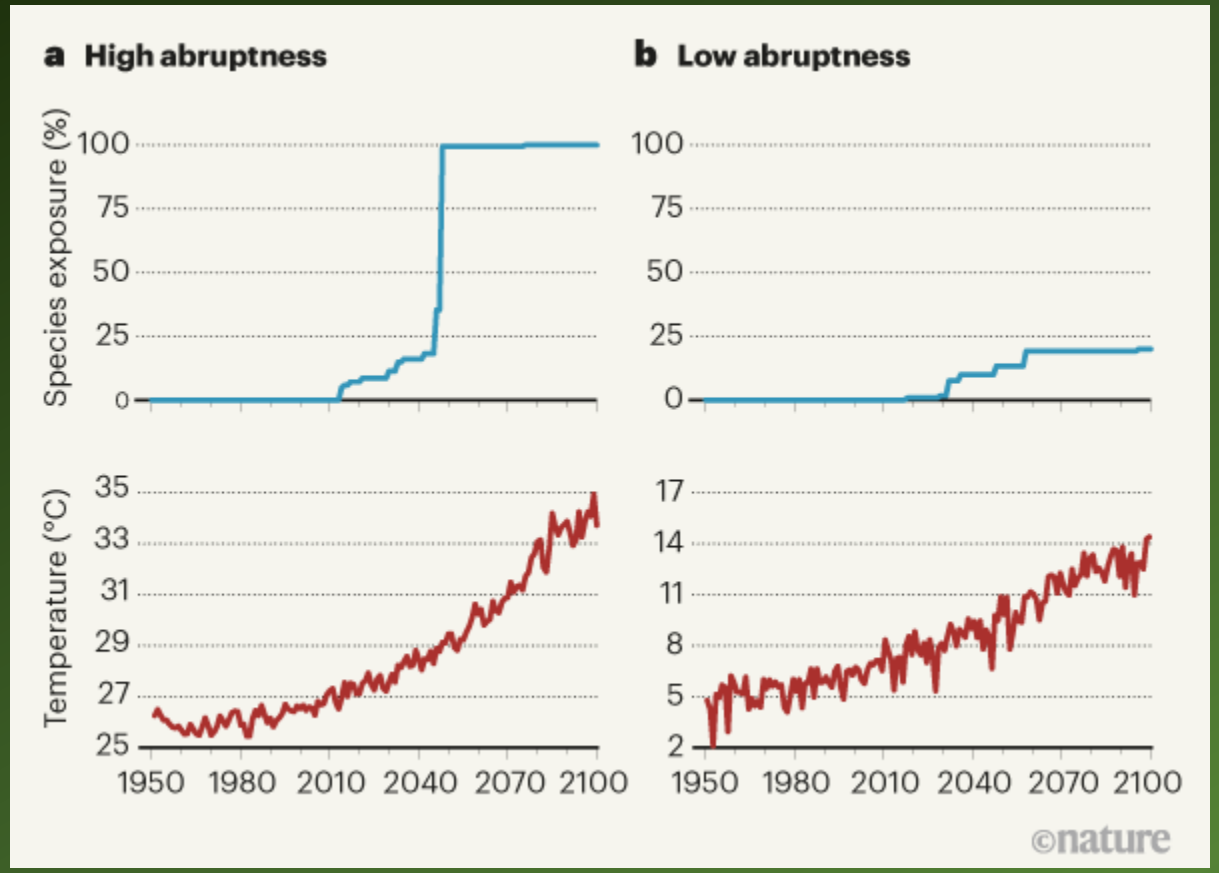
Climate Change and Food Scarcity



Paul Voosen Science 2020;368:226-229

Science AAAS

Global warming & habitat loss: At 1.5º C



6% for insects

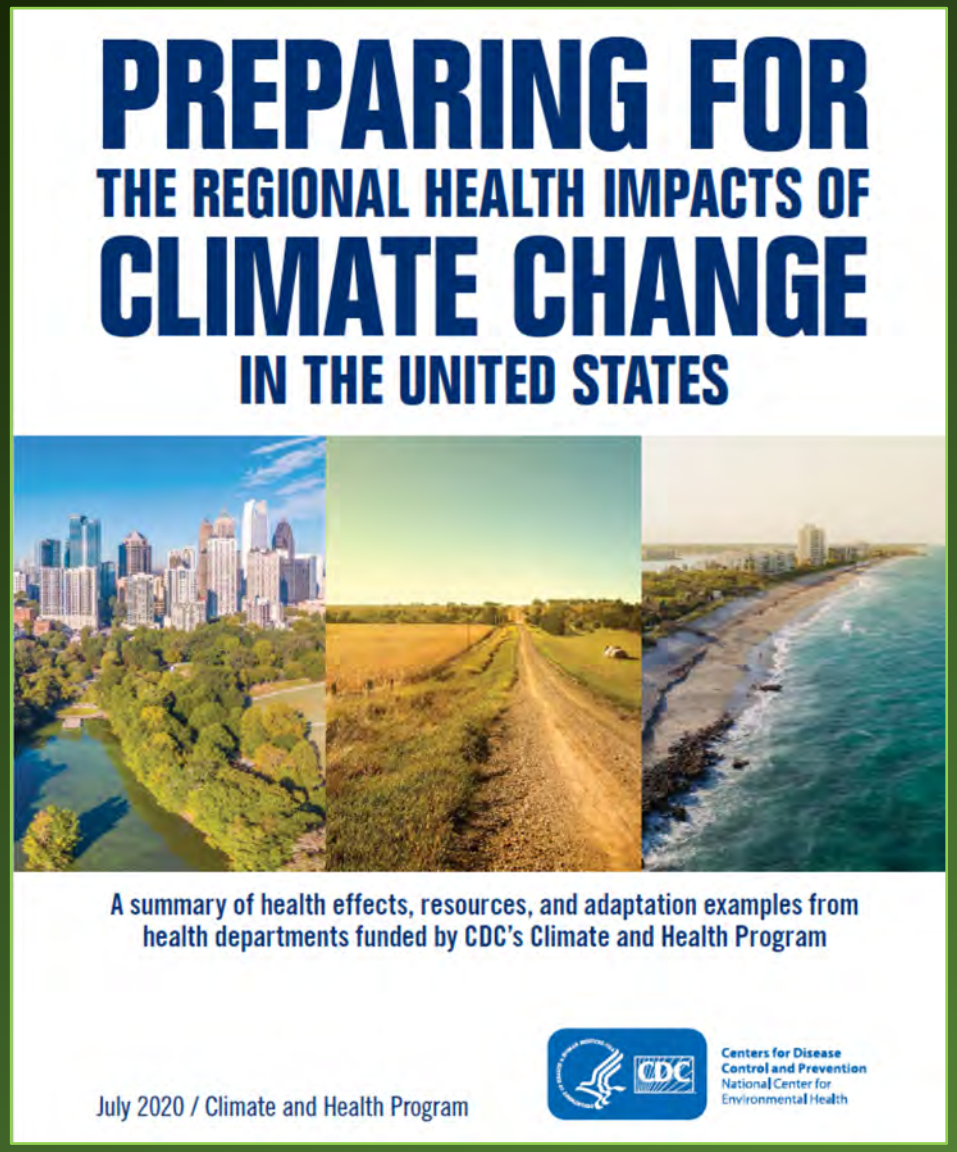
8% for plants

4% for vertebrates by 2100

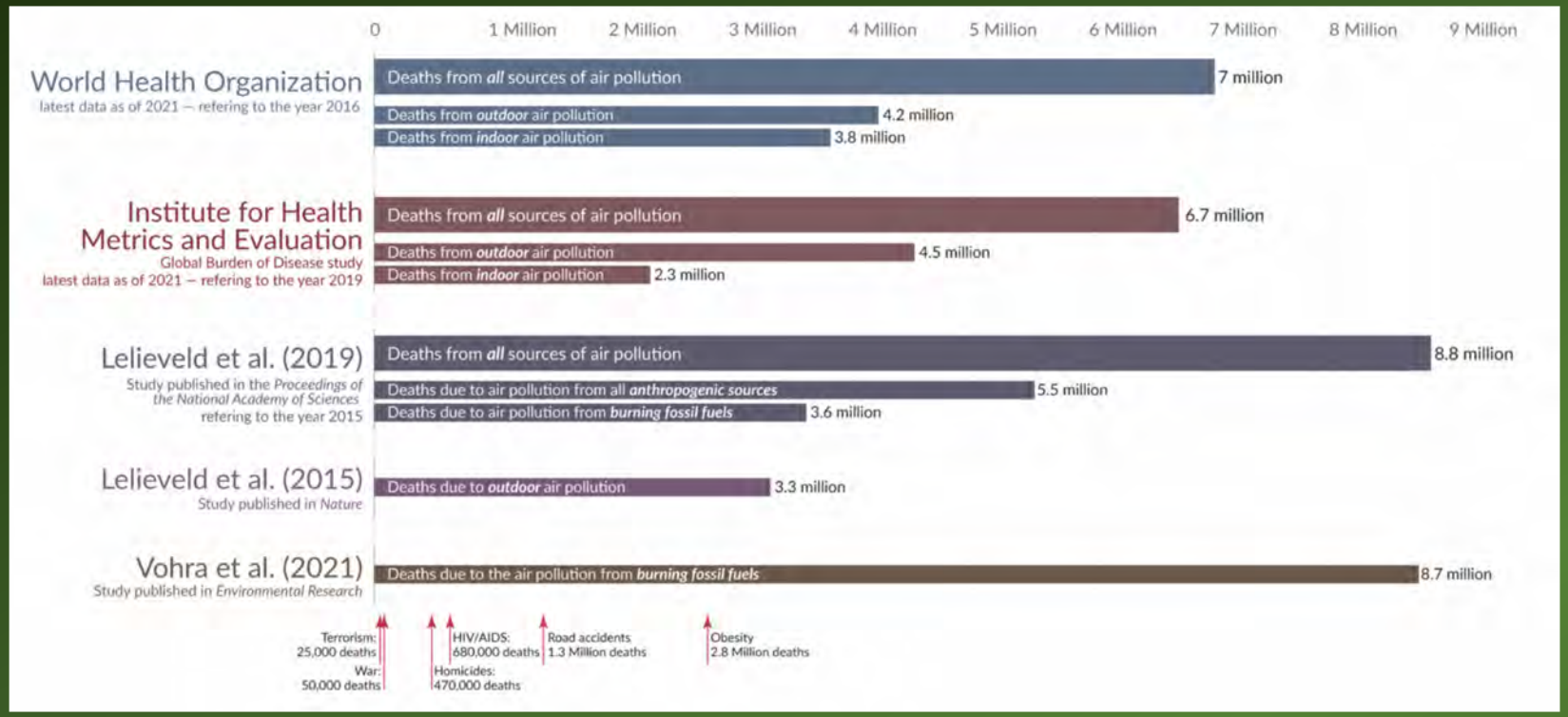
The risks at 2º C >double

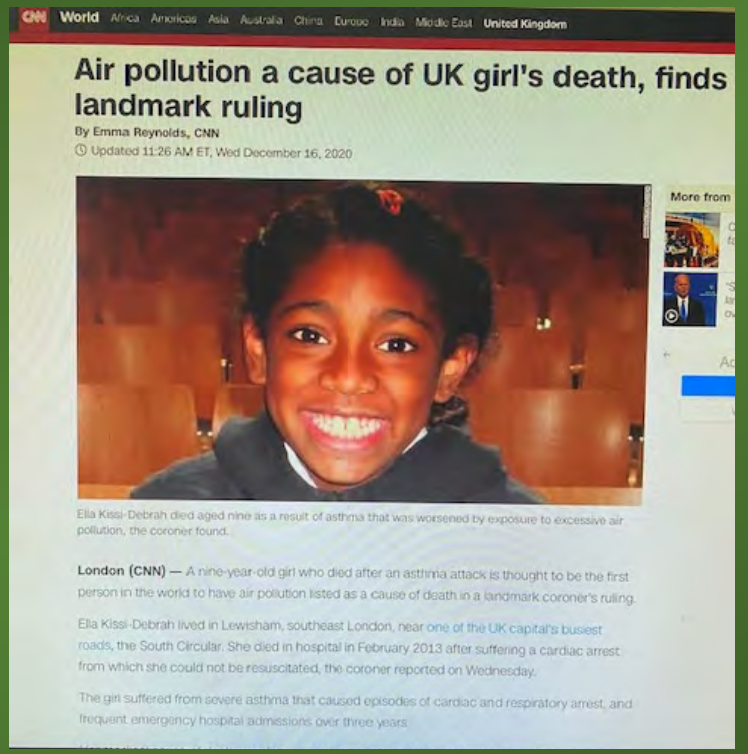
4º C warming are ~10 times larger.

Health Impacts of Climate Change



Air Pollution the Driver for Climate Change also Kills Millions Yearly





Which of the following Clinical Conditions are Expected to Increase with Climate Change?

A Suicide

B Heat Stroke

C Vector bone diseases

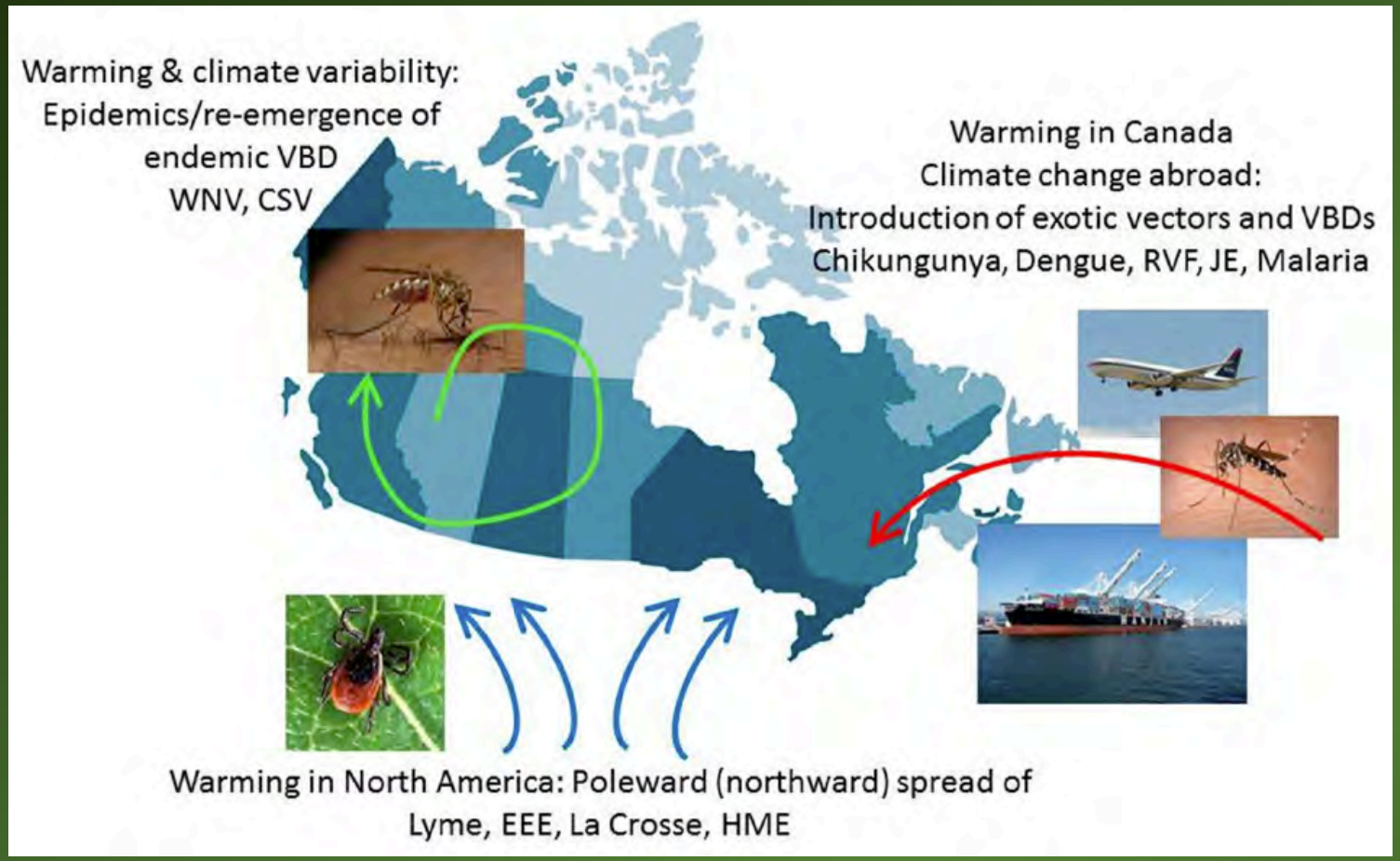
D Hypothermia

Climate Change and Vector Borne Infectious Disease Dynamics

- The Ebola outbreak in Sierra Leone, Liberia and Guinea
- Zika Virus affecting Latin America, Caribbean, Southern Florida and Texas
- Increased avian malaria in higher altitude and Latitudinal range
- Increased VBD affecting health of domestic animals: (Trypanosomiasis, Rift Valley fever and blue tongue)

Caminade C. Ann. NY. Acad Sci 2019

Vector Borne Disease & Climate change



Nicholas H Ogden, Environ Microbiol 2020

Mechanisms: Increased Vectoral Capacity

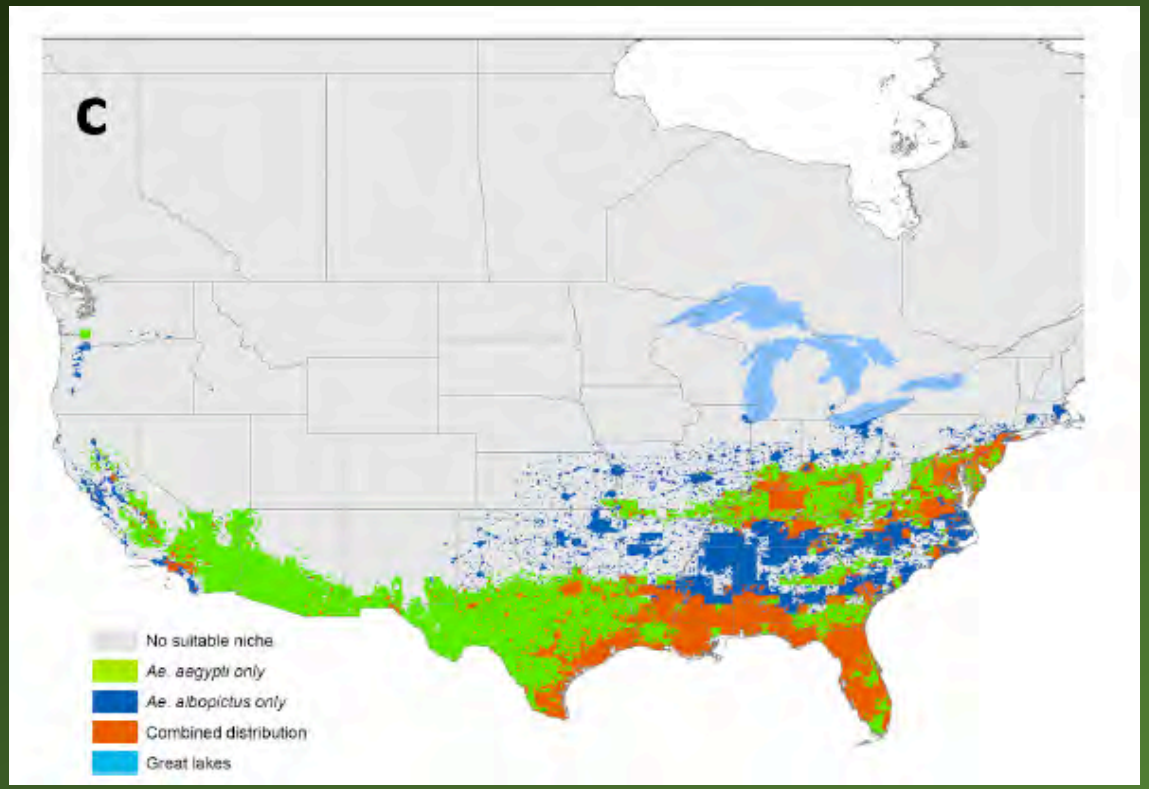
- Flooding can hamper disease control measures like vector control ineffective
- Increased Larval development from water stagnation,Temp., and increased humidity
- Vector biting rates increase with higher temperature up to a threshold
- Increased transmission and replication of pathogens within vectors
- Migration of animals vectors to pathogens

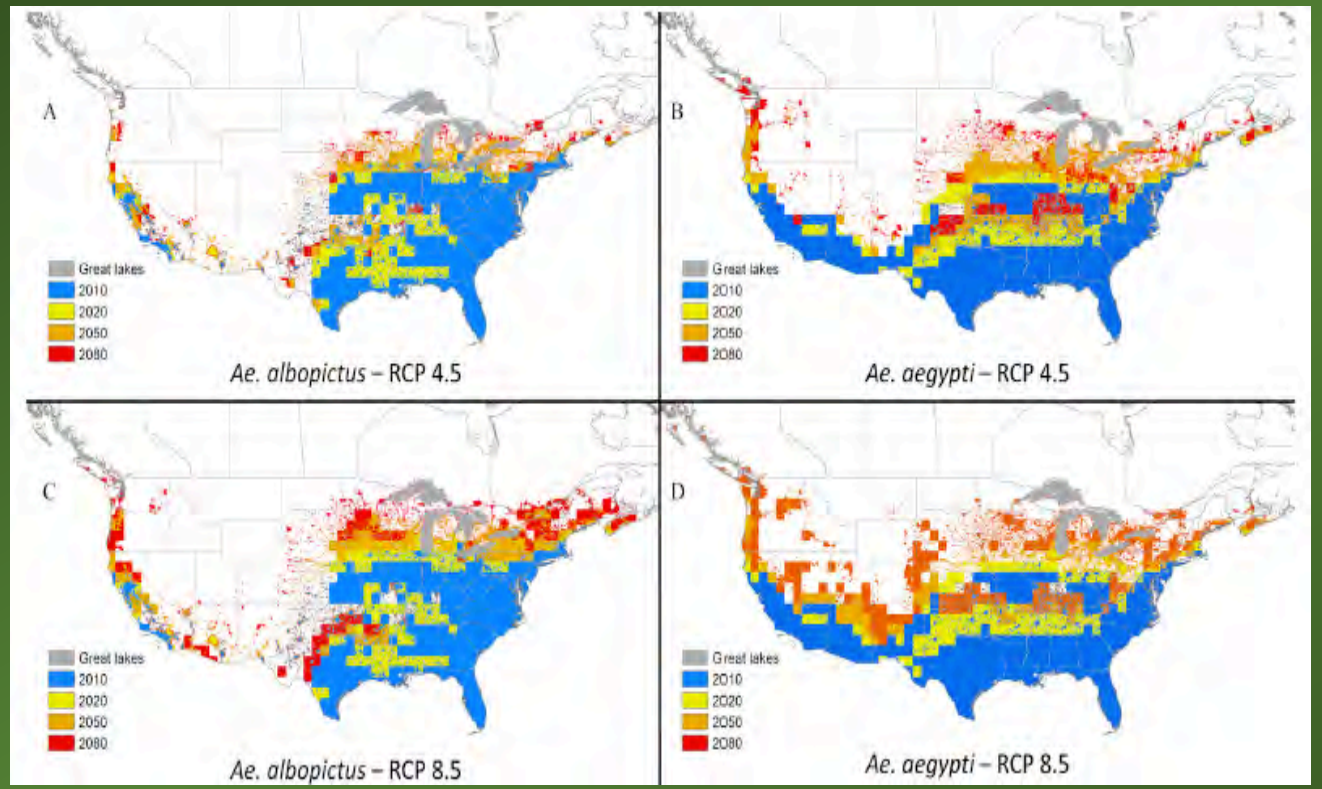
Caminade C ,McIntyre M, AE Jones,
Ann N Y Acad Sci, 2019

Its Happening Slowly but Surely

- **Chikungunya reported in southern France in 2010 and 2014 and local transmission in 2014 in USA**
- **Dengue transmission in Croatia in 2010 and China in 2014**
- **Limited local transmission of ZIKA occurred in Texas and South Florida 2017**

Current and Predicted Distribution of *A. Aegypti* and *A. Albopictus*





Environmental Health Perspective 2020

Autochthonous Arbovirus Infections:

COMMUNITY

Dispose of tires before they become breeding grounds

Suzanne Michaels For the Sun-News

Published 12:29 p.m. MT Feb. 9, 2016

View Comments

Arboviruses: Aedes Species

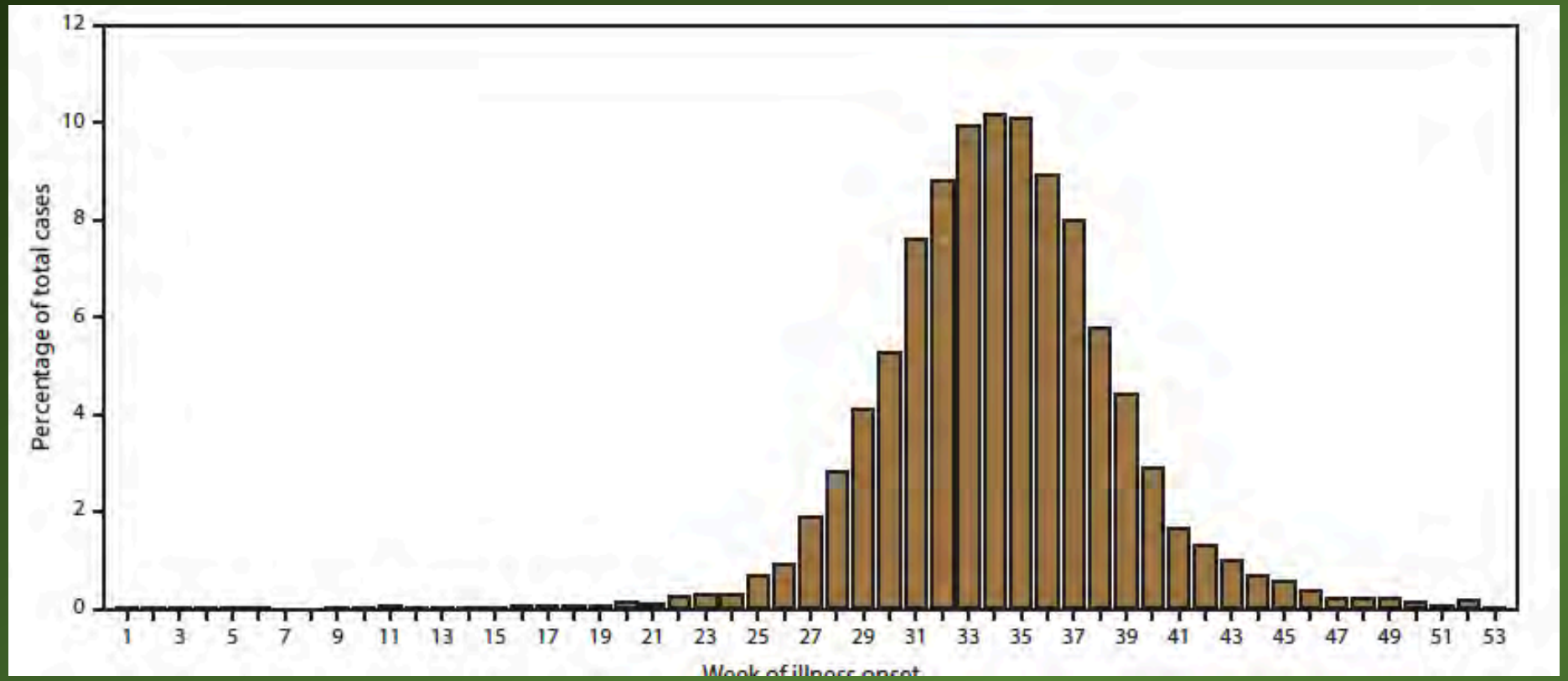
- Dengue
- Chikungunya
- Yellow fever
- Zika
- West Nile

Caminade C ,McIntyre M, AE Jones,
Ann N Y Acad Sci, 2019

West Nile Virus: Culex Mosquitoes

- Most common Encephalitic virus
- Confined to Africa
- First case appeared in New York in 1999
- Spread to California in 2003
- Large breakout occurred in Russia in 2000
- Mild Winter combined with draught increased transmission in US
- Extrinsic Incubation period of WNV in Culex shortened with climate change

Percentage of Cases by week from 2009-20018 (n=21869)



Expect more cases with prolonged summer time

Climate Change and Malaria

- Local Transmission of P. Vivax in Greece 2009-2010
- Limited transmission of P.Vivax in Spain and Italy 2017
- Dramatic re-emergence in Anhui province of China since 2000

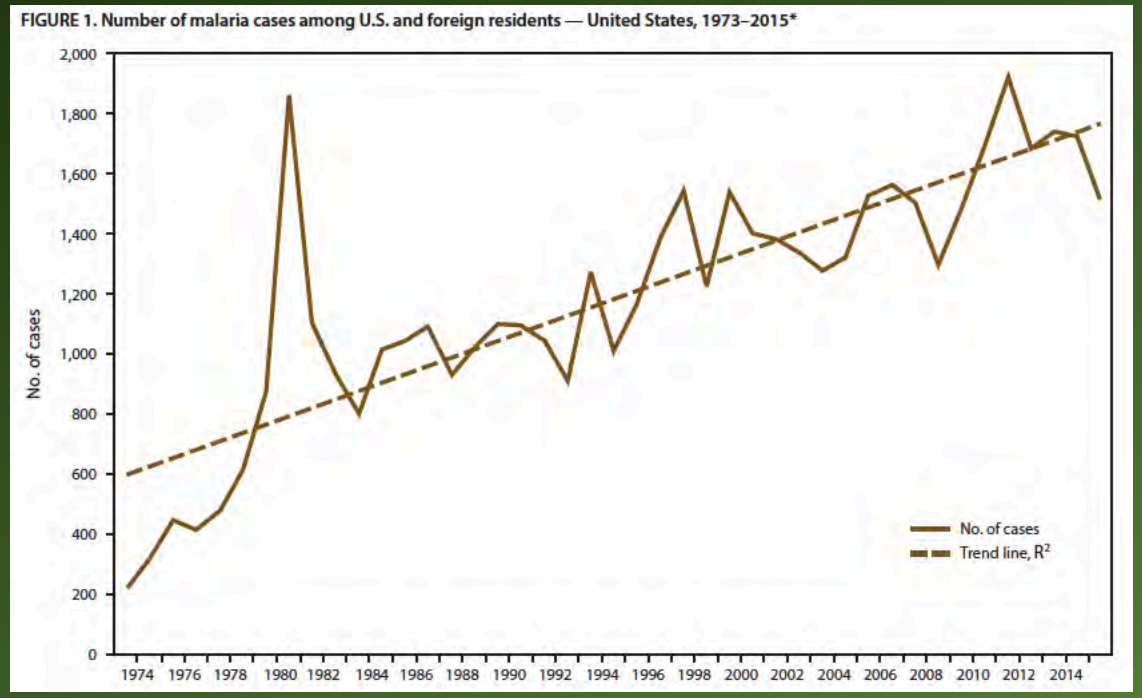
Caminade C. Ann.N.Y.Acad Sci 2019

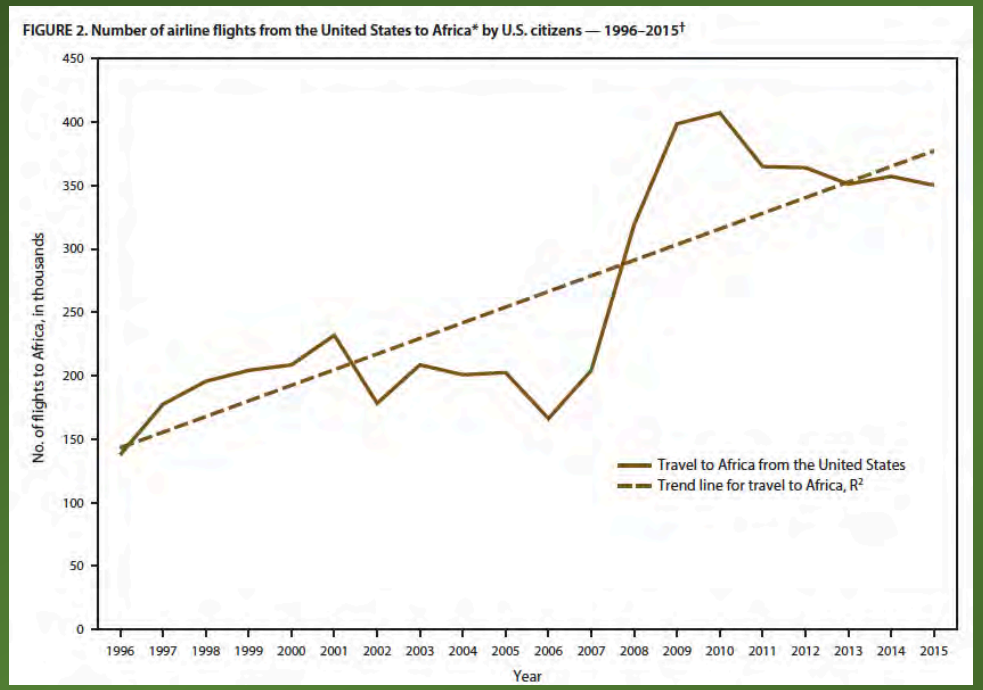
Malaria:

- Falciparum is increasing in tropical highland regions (East Afrrica, Nepal, Columbia)
- Malaria affecting reptiles and birds are reported in Alaska
- Occasionally (Plasmodium Knowlesi small primates) can infect humans
- As tropical temperature becomes unbearable for mosquito vectors, it is predicted to to shift to sub-Saharan Africa by end of 21st centaury.

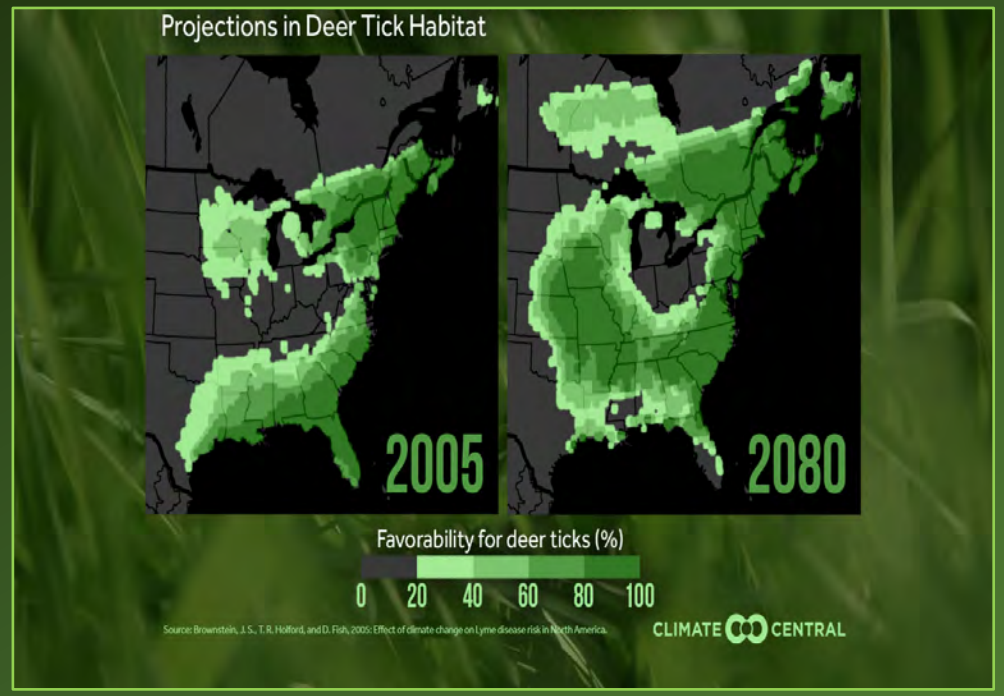
Gething PW. Nature 2010
Walker PG, Lancet Global Health 2016

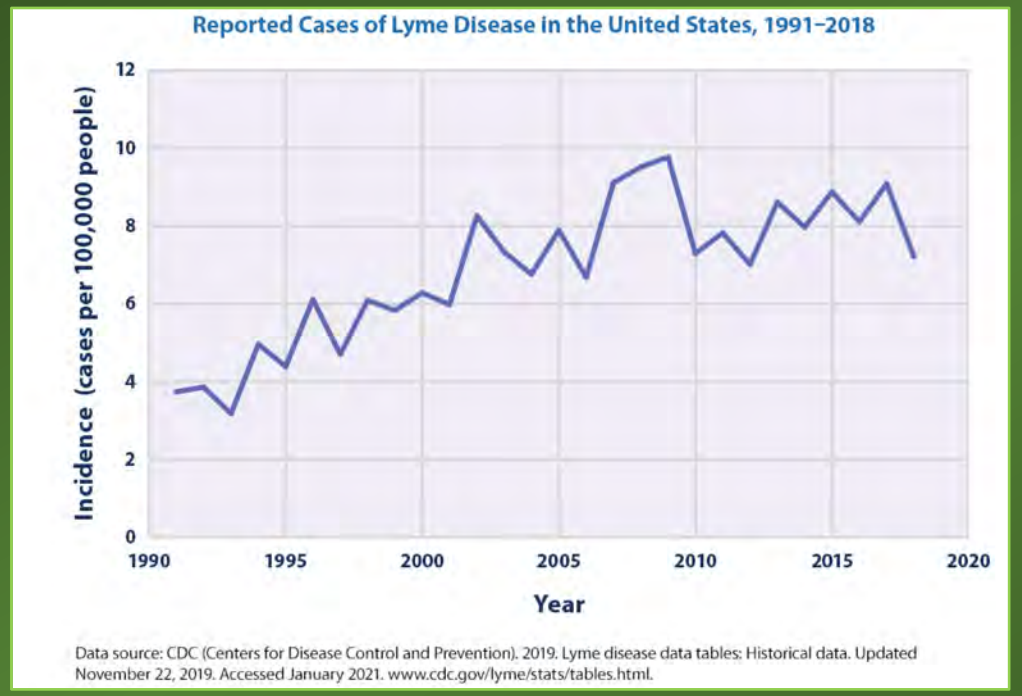
Malaria in US are Travel Related



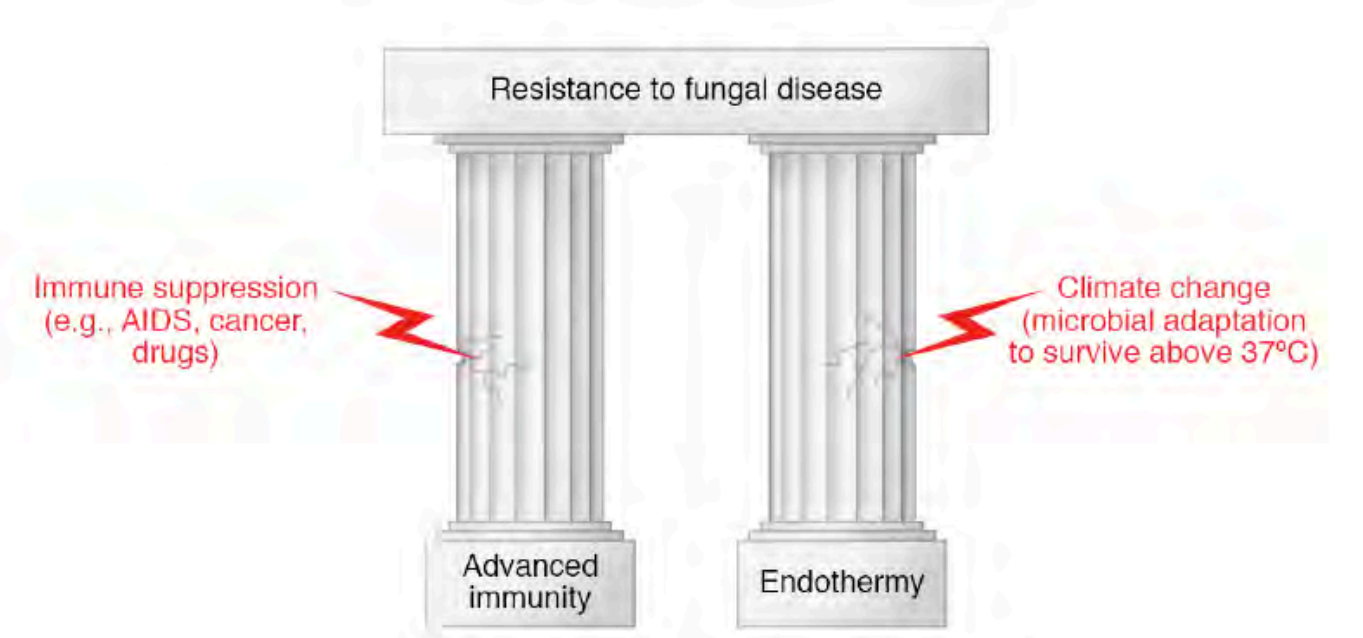


Ticks on the March



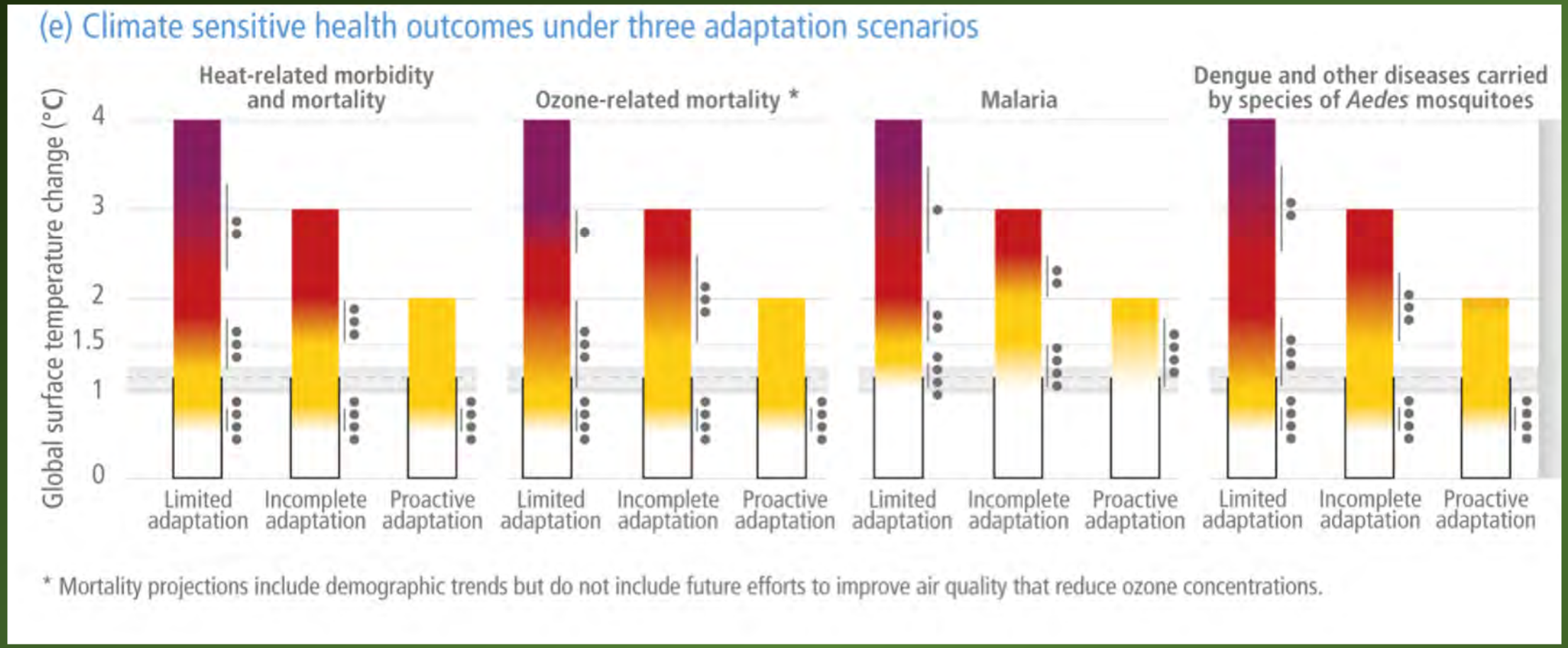


Pillars of Resistance to Fungal Disease



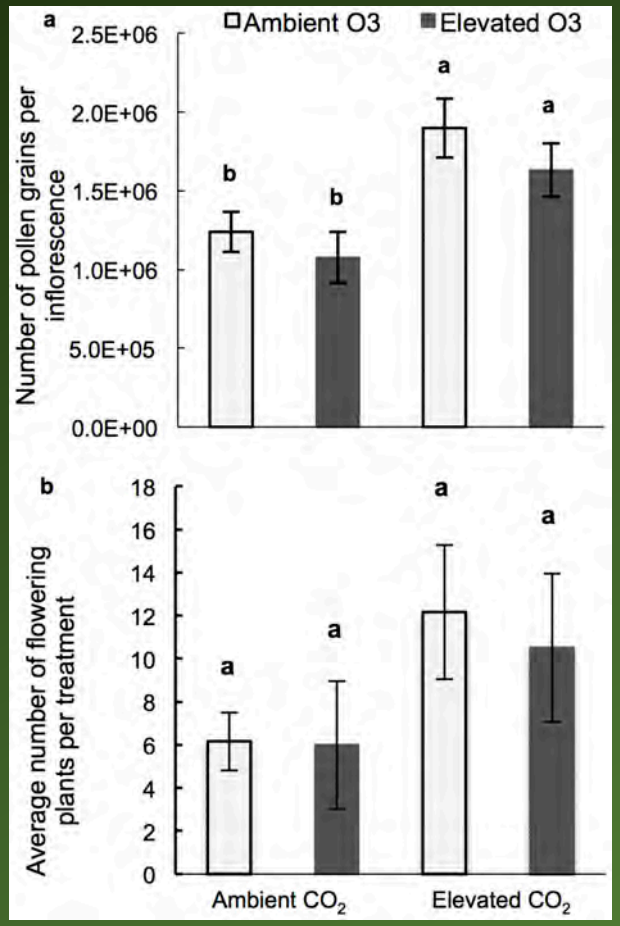
Casadevall A. JCI 2020

Health Outcomes & Adapt or Perish



IPCC 2021

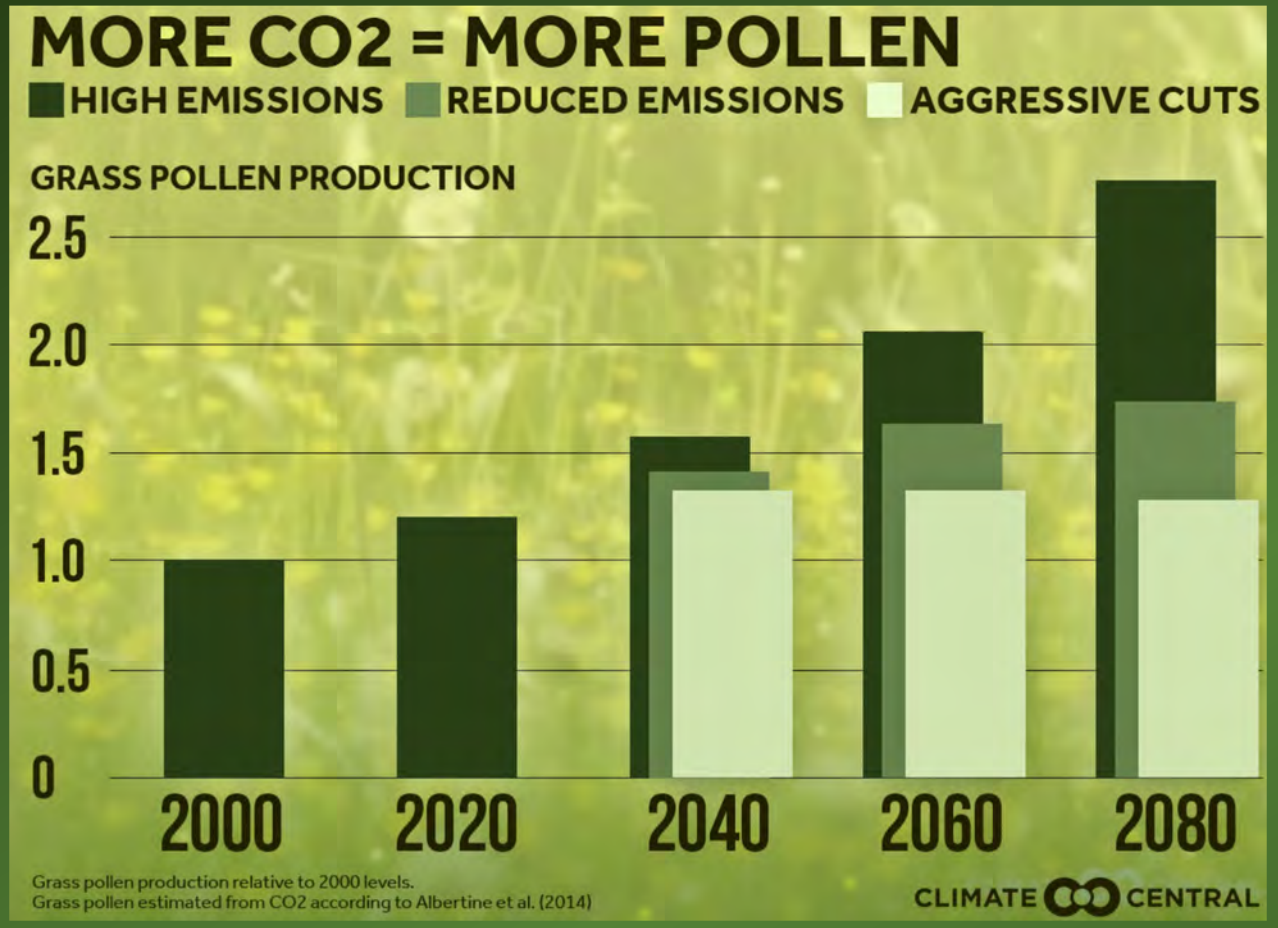
CO_2 increase and Allergic Disease



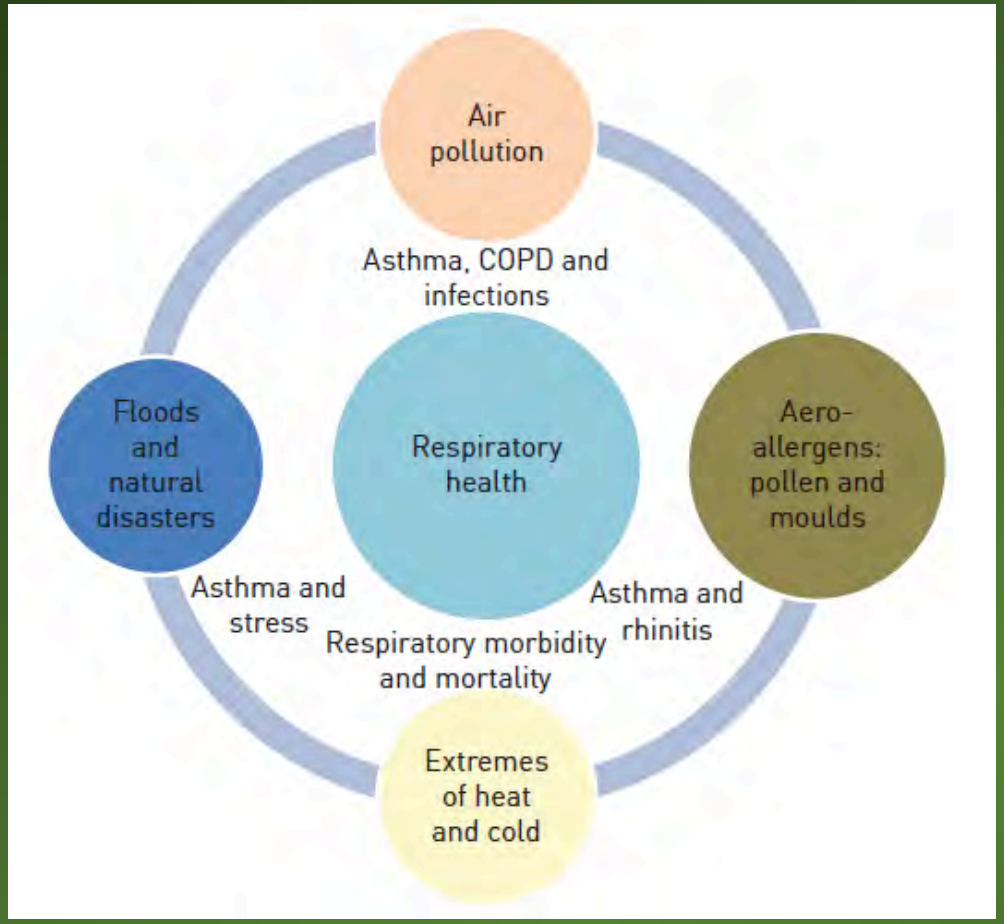
Airborne grass pollen concentrations will increase in the future up to ~200%.

J Albertine et.al Plos One, 2014

Combined Effect of CO2 & Temperature Increase

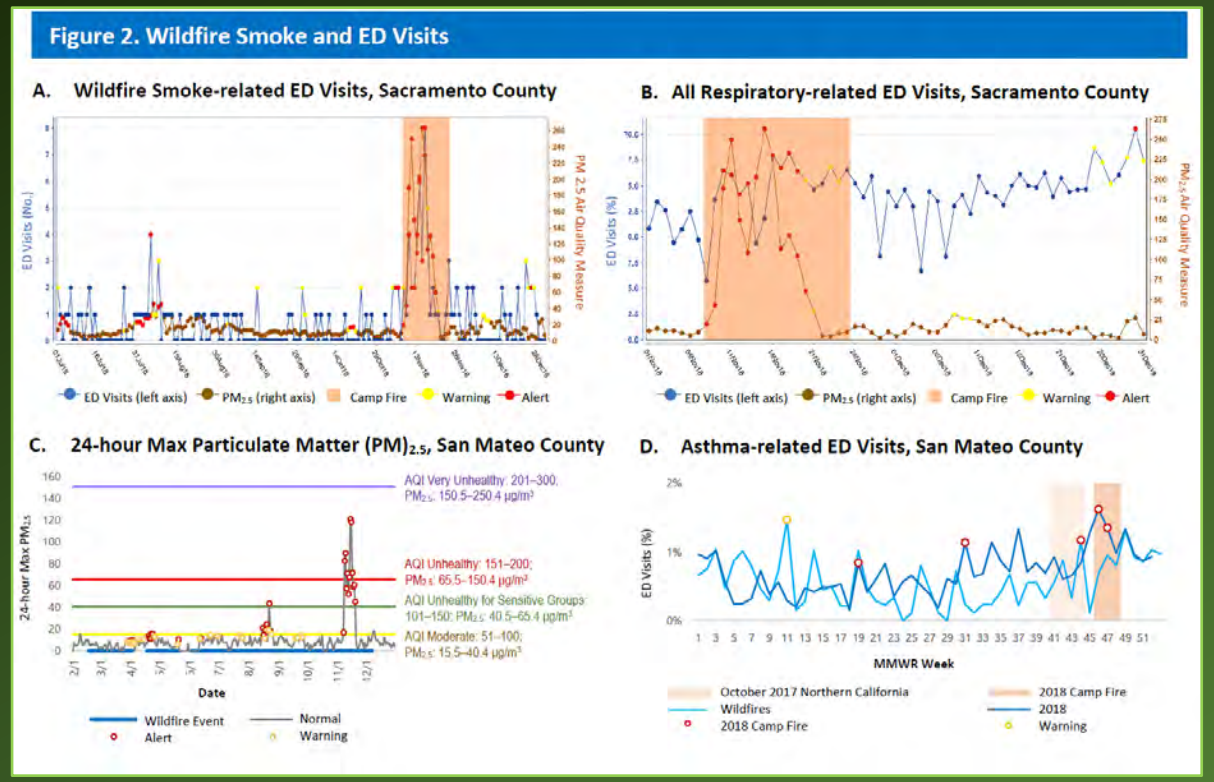


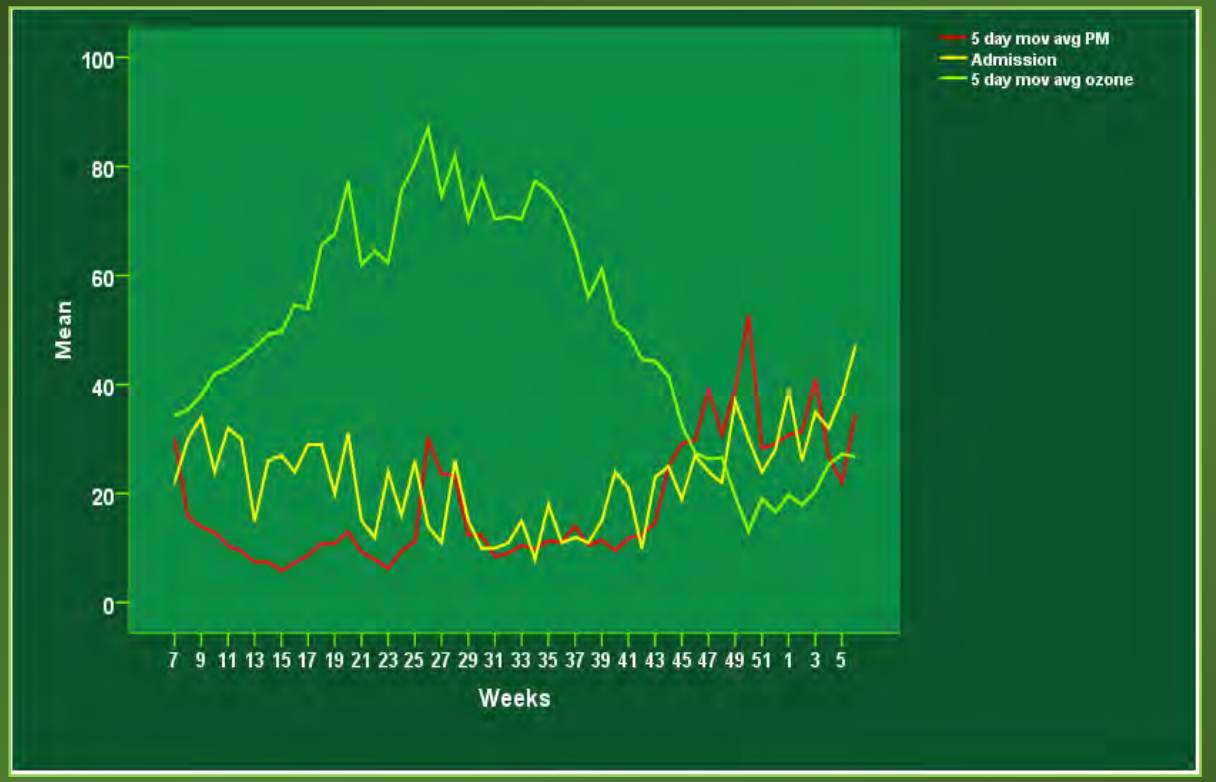
Climate Change & Respiratory Disease



G D'Amato, Eur Respir Rev 2014

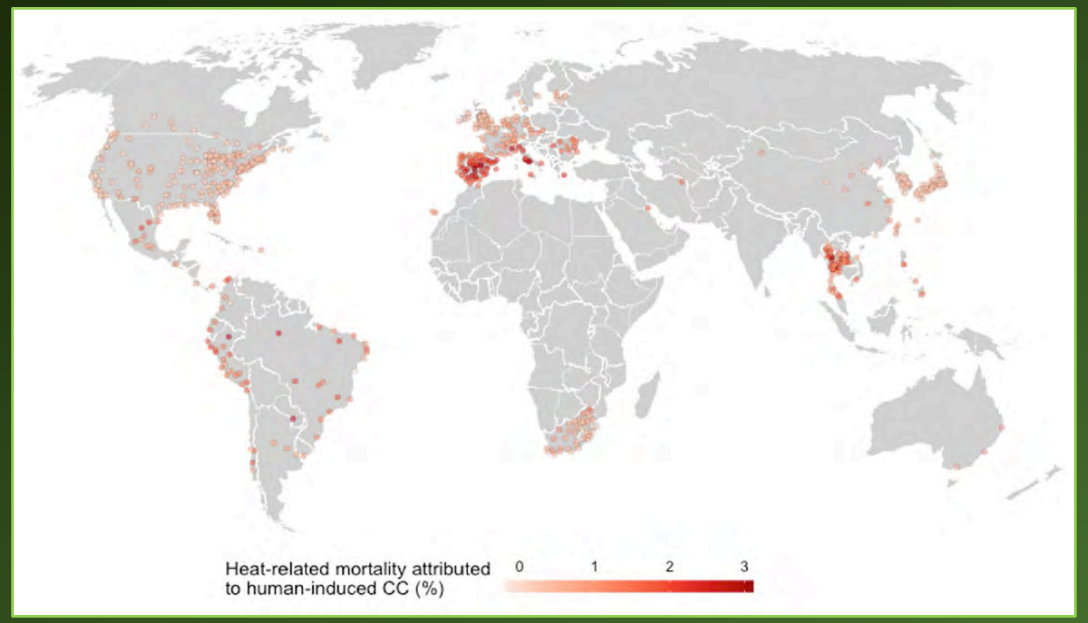
National Syndromic Surveillance CDC



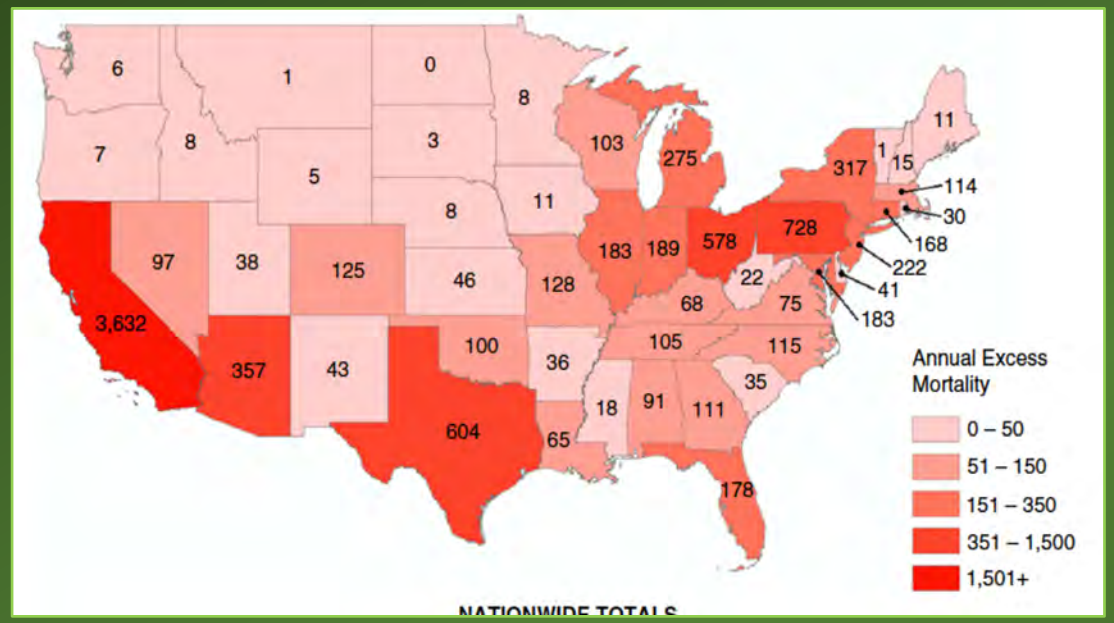


J Patel & Vempilly Joseph, Chest 2009

Heat Related Mortality attributable to Climate Change & Air Pollution

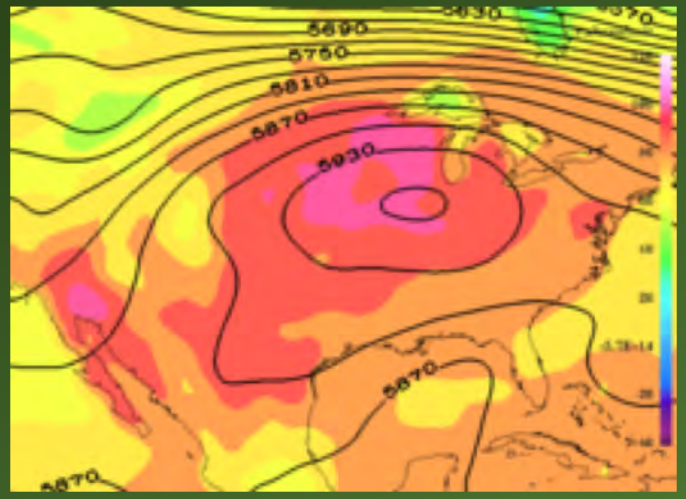


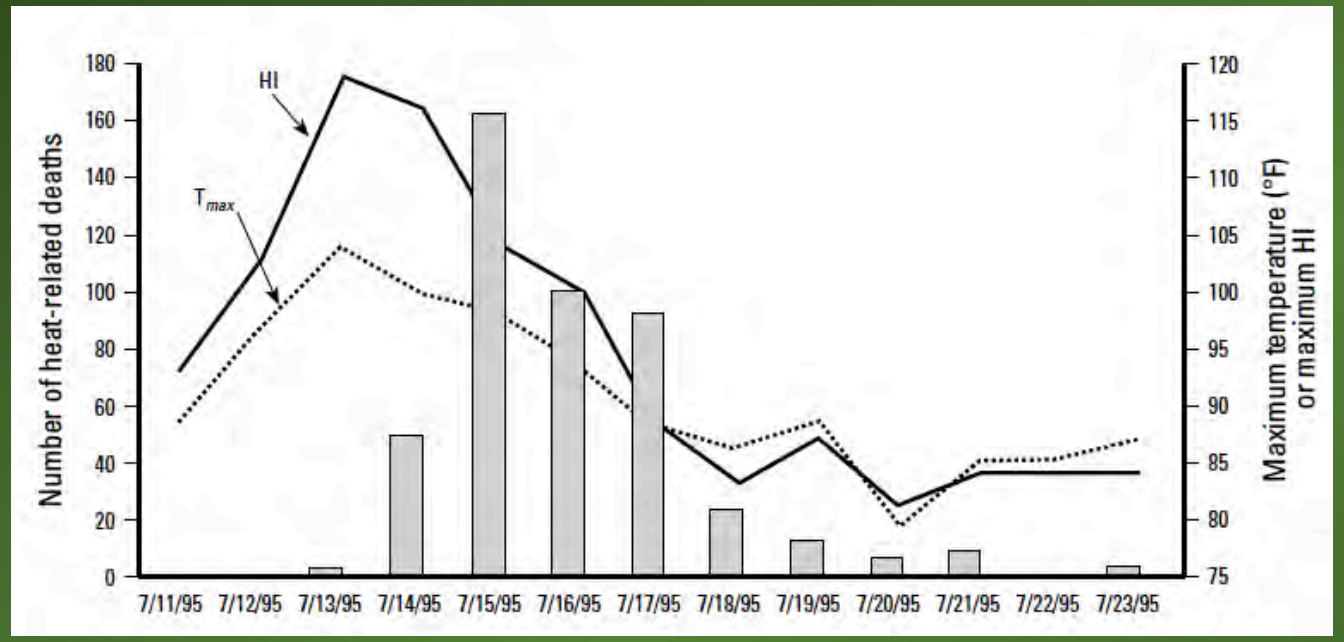
Europe PMC Founders group
Nature Climate Change, June 2021



ATS & Marron report
Air Pollution and excesses Mortality, 2016

Heat Related Mass Causality , Chicago 1995 n=739

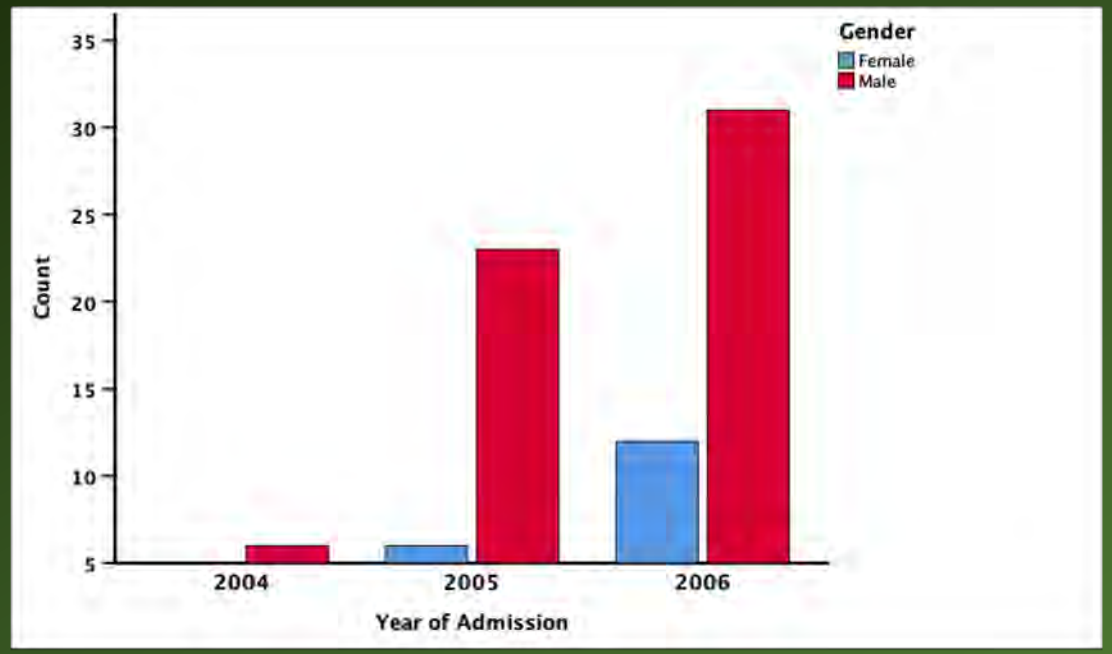


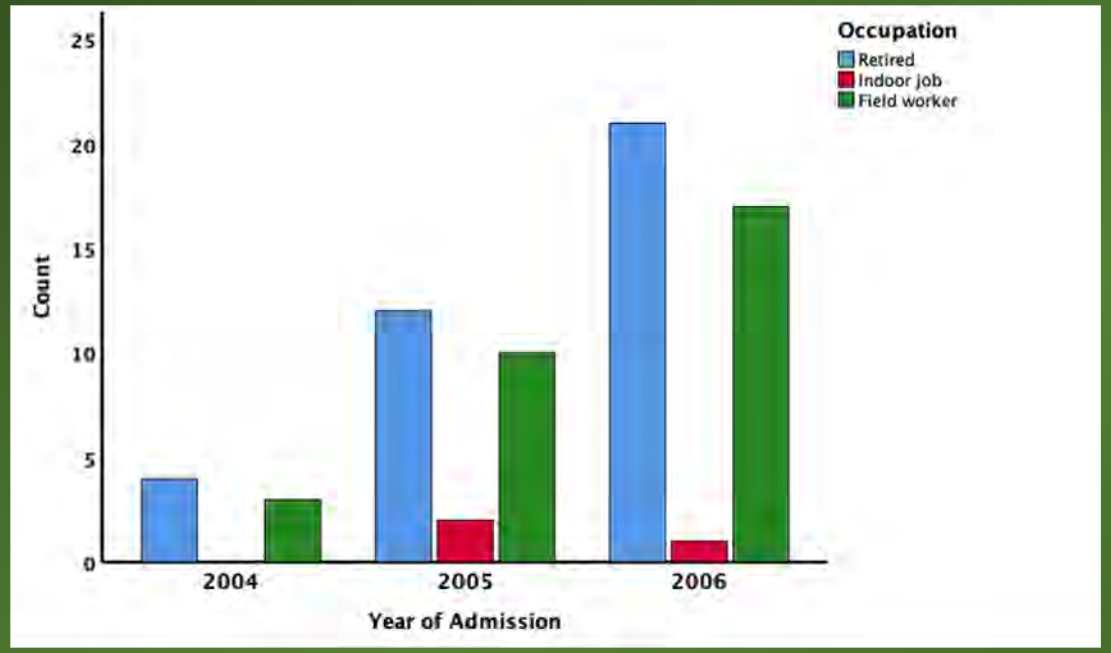


MacGeehin and Mirabelli Environ Health Prespect , 2001

California Heat Wave 2006: Impact of Hospitalization and ER Visits

Heat Strokes in Fresno CA 2004 to 2006
Fatality 225





Joseph Vempilly &
ACP Abstract 2008

Climate Change- A Health Emergency

November 2018, the UC Davis, Burn Center

David Greenhalgh, professor and chief of the Burn Division, UC Davis Department of Surgery, was when the chaos began. Within the next 24 hours, with fires raging, 12 new burn patients were rushed to his facility

Solomon CG and LaRocque RC, NEJM 2019

Increasing Frequency of Extreme Winter with Polar Warming

REPORT

CLIMATE DYNAMICS

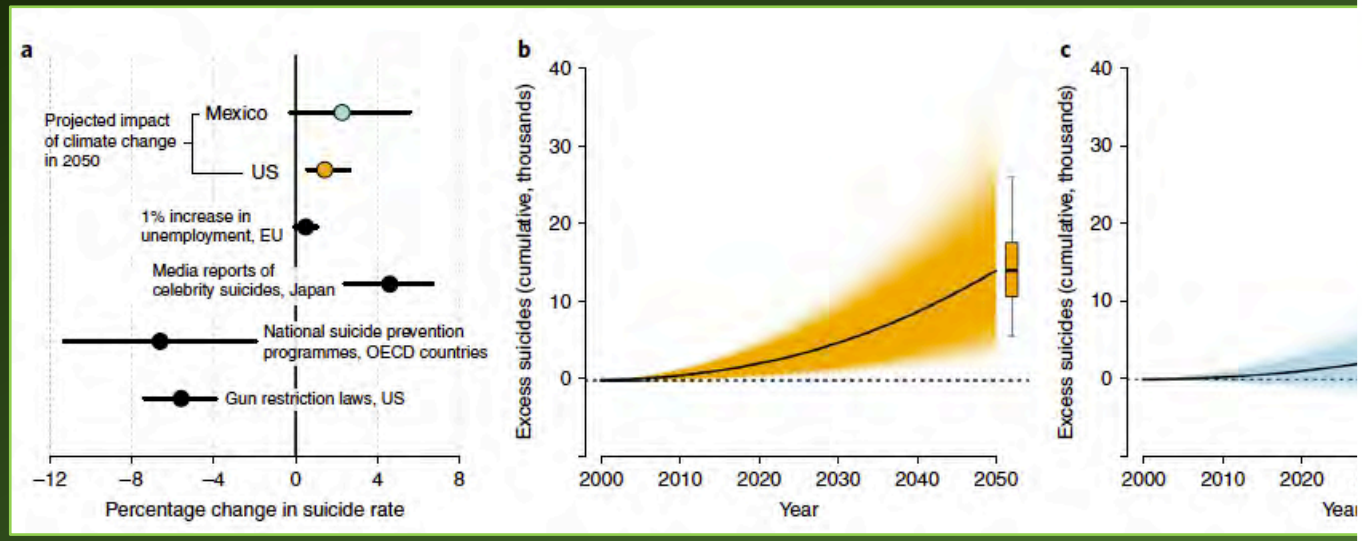
Linking Arctic variability and change with extreme winter weather in the United States

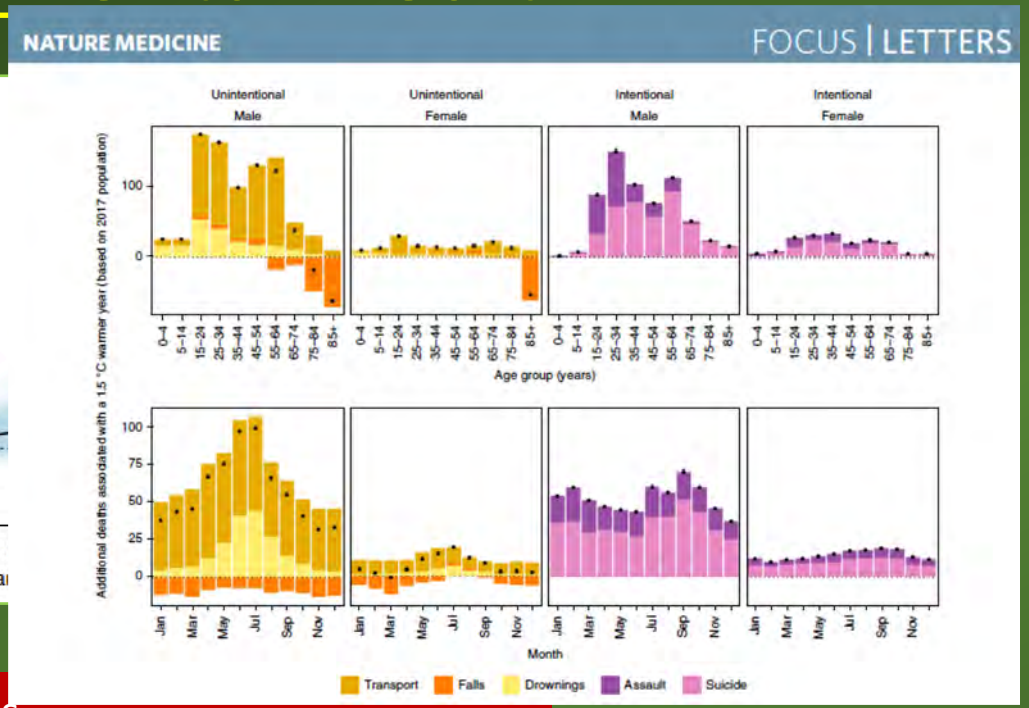
Judah Cohen[1,2]*, Laurie Agel[3], Mathew Barlow[3], Chaim I. Garfinkel[4], Ian White[4]

The Arctic is warming at a rate twice the global average and severe winter weather is reported to be increasing across many heavily populated mid-latitude regions, but there is no agreement on whether a physical link exists between the two phenomena. We use observational analysis to show that a lesser-known stratospheric polar vortex (SPV) disruption that involves wave reflection and stretching of the SPV is linked with extreme cold across parts of Asia and North America, including the recent February 2021 Texas cold wave, and has been increasing over the satellite era. We then use numerical modeling experiments forced with trends in autumn snow cover and Arctic sea ice to establish a physical link between Arctic change and SPV stretching and related surface impacts.

Science 2021

Climate Change and Mental Health





Mental well being deteriorates during warmer periods

Projection : 9 to 40 thousand additional suicides in US and Mexico by 2050

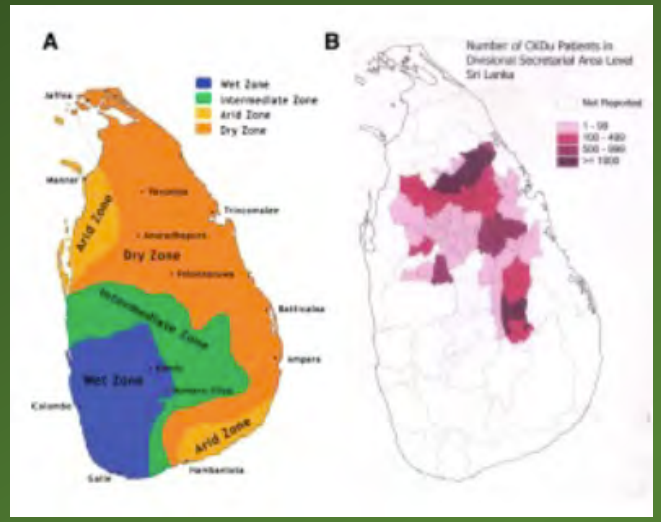
M. Burke: Nature Climate Change

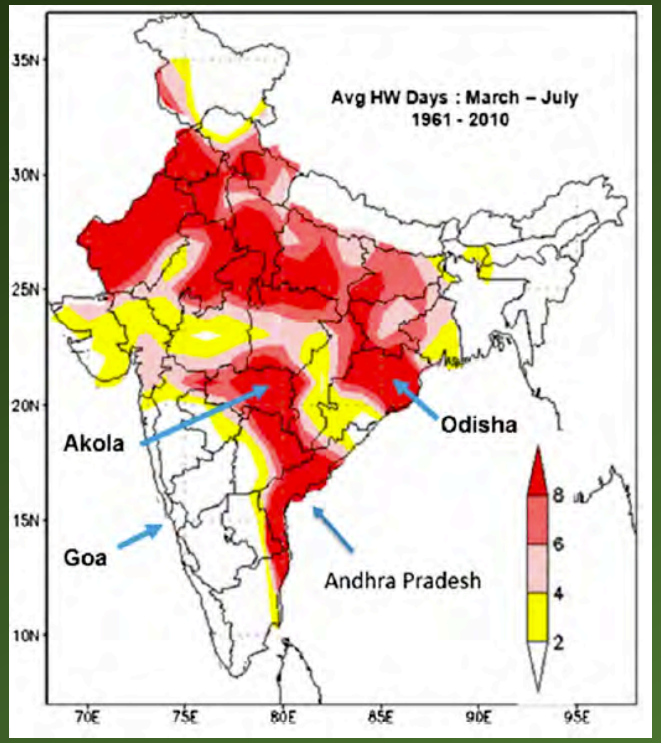
Heat Stress Nephropathy

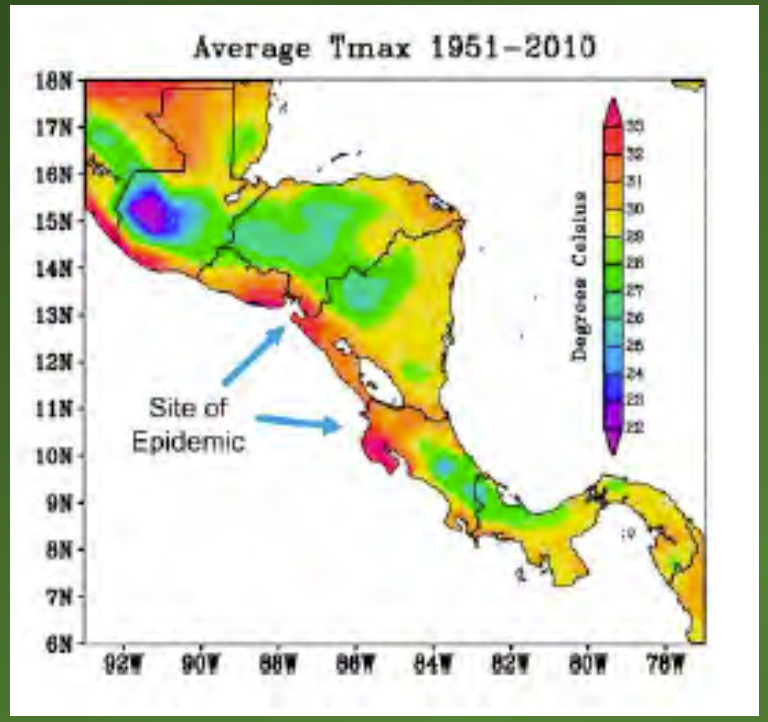
Clin J Am Soc Nephrol. 2016 Aug 8; 11(8): 1472–1483. PMCID: PMC4974898
Published online 2016 May 5. doi: 10.2215/CJN.13841215 PMID: 27151892

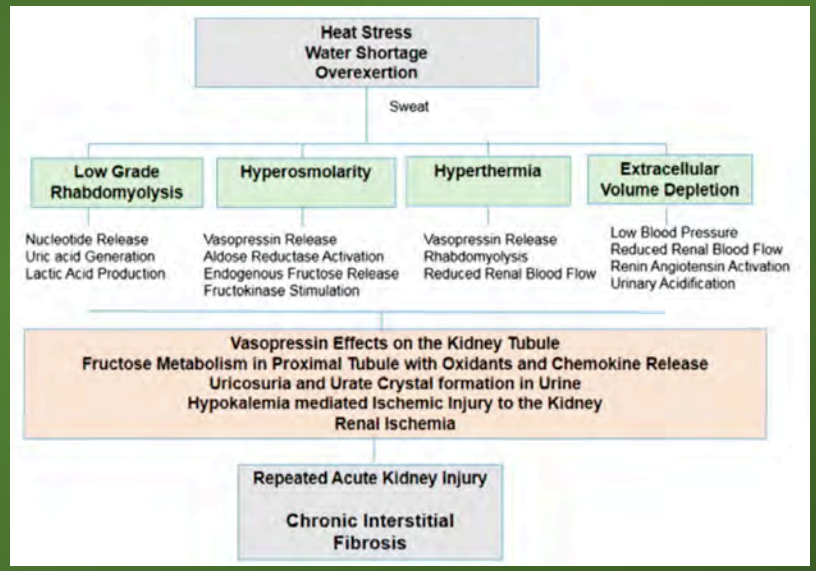
Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy

Jason Glaser, Jay Lemery, Balaji Rajagopalan, Henry F. Diaz, Ramón García-Trabanino, Gangadhar Taduri,

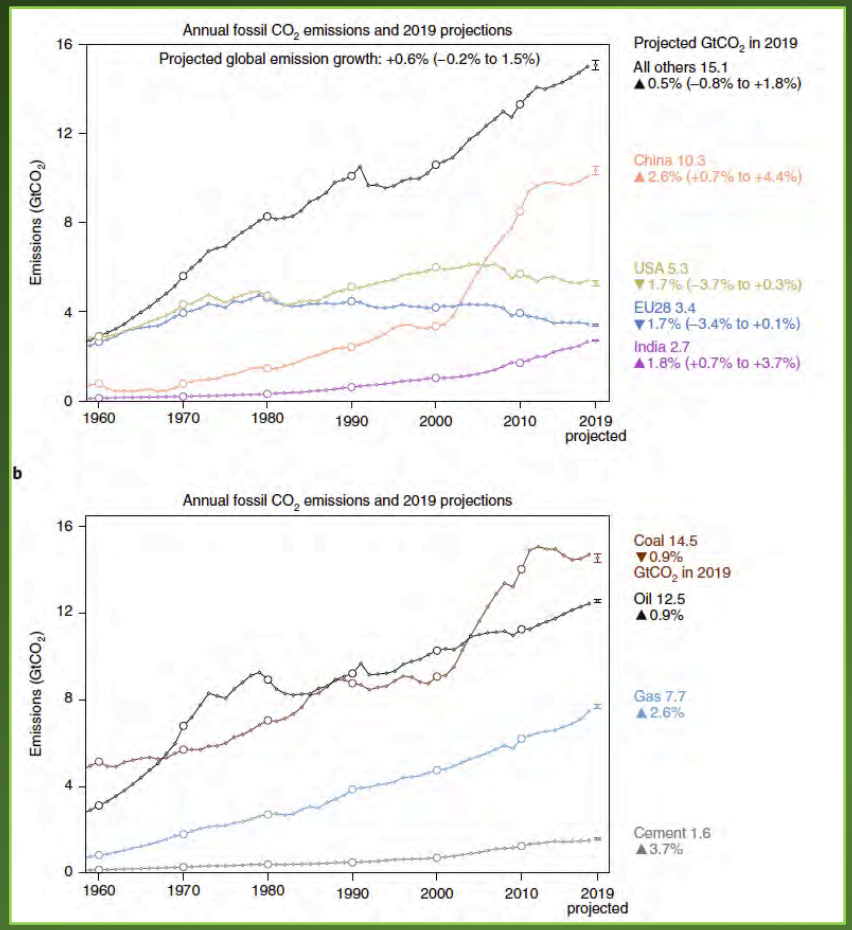






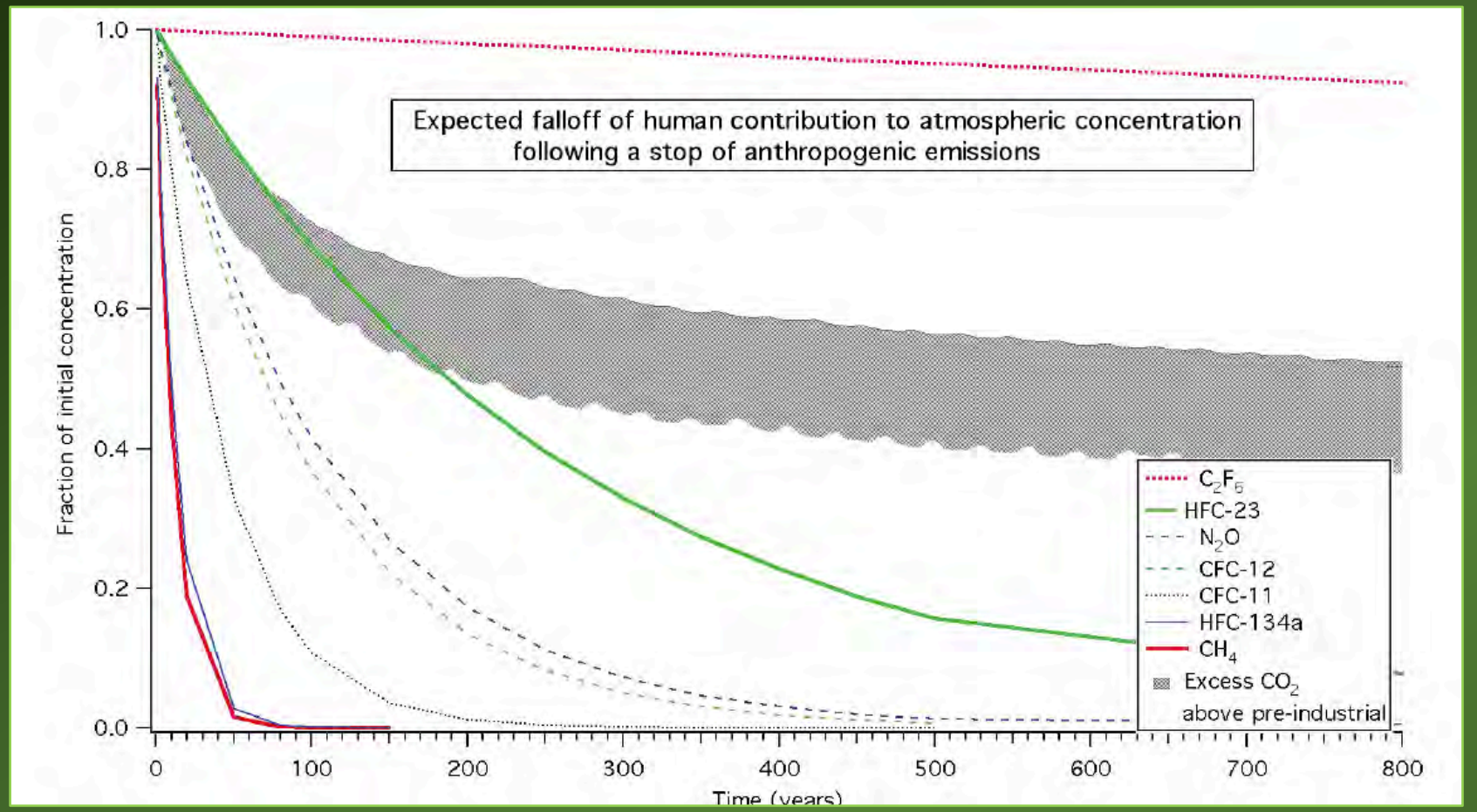


While We Debate Climate, Climate Change is Galloping



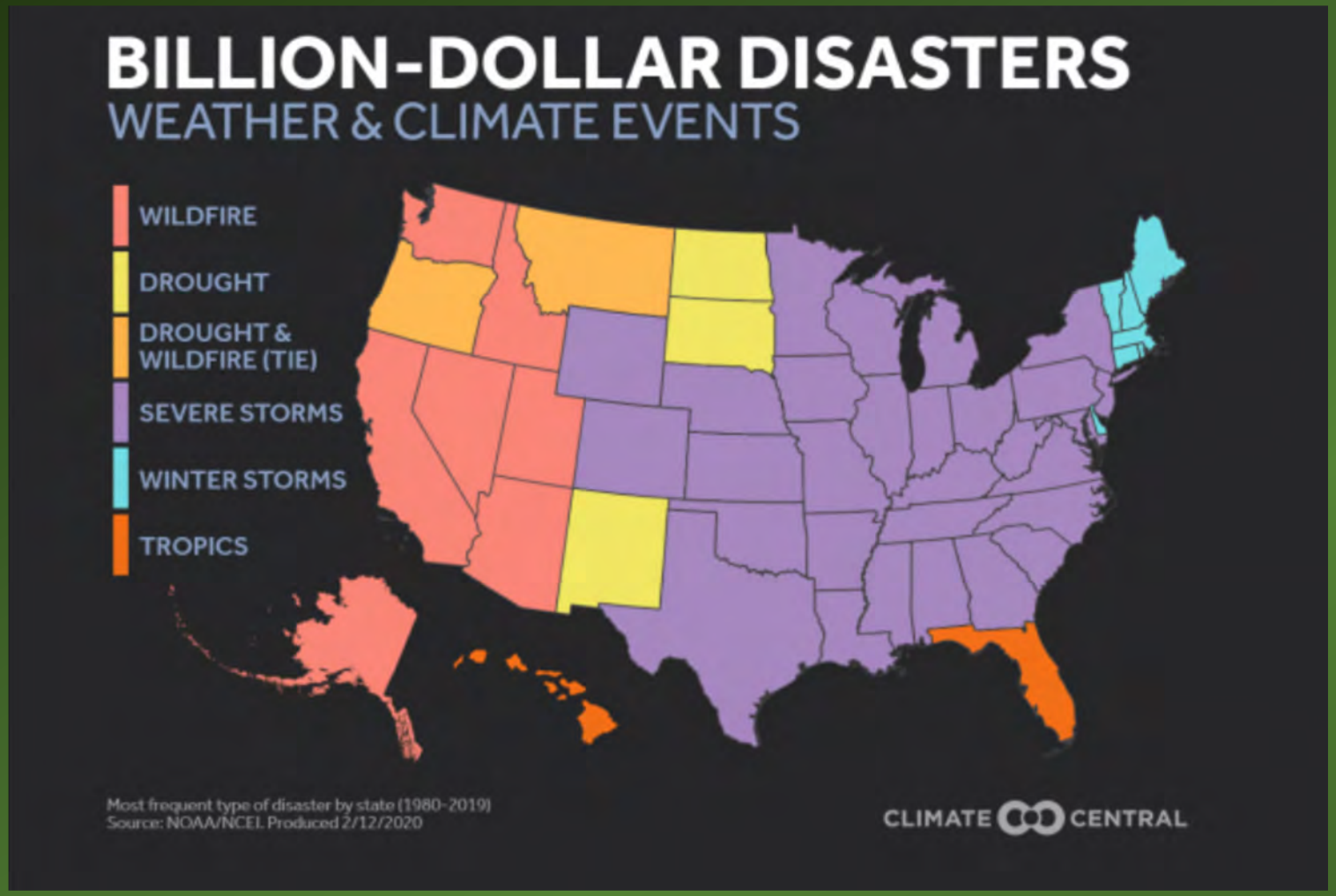
G. Peters, Nature Climate Change 2019

Even if We Stop Producing CO_2, It will take Several Centuries to Stabilize



Solomon et al., PNAS, 2009

Insurance Companies Knew it all



Urgent Solutions to Mitigate the Armageddon

Intergenerational problem

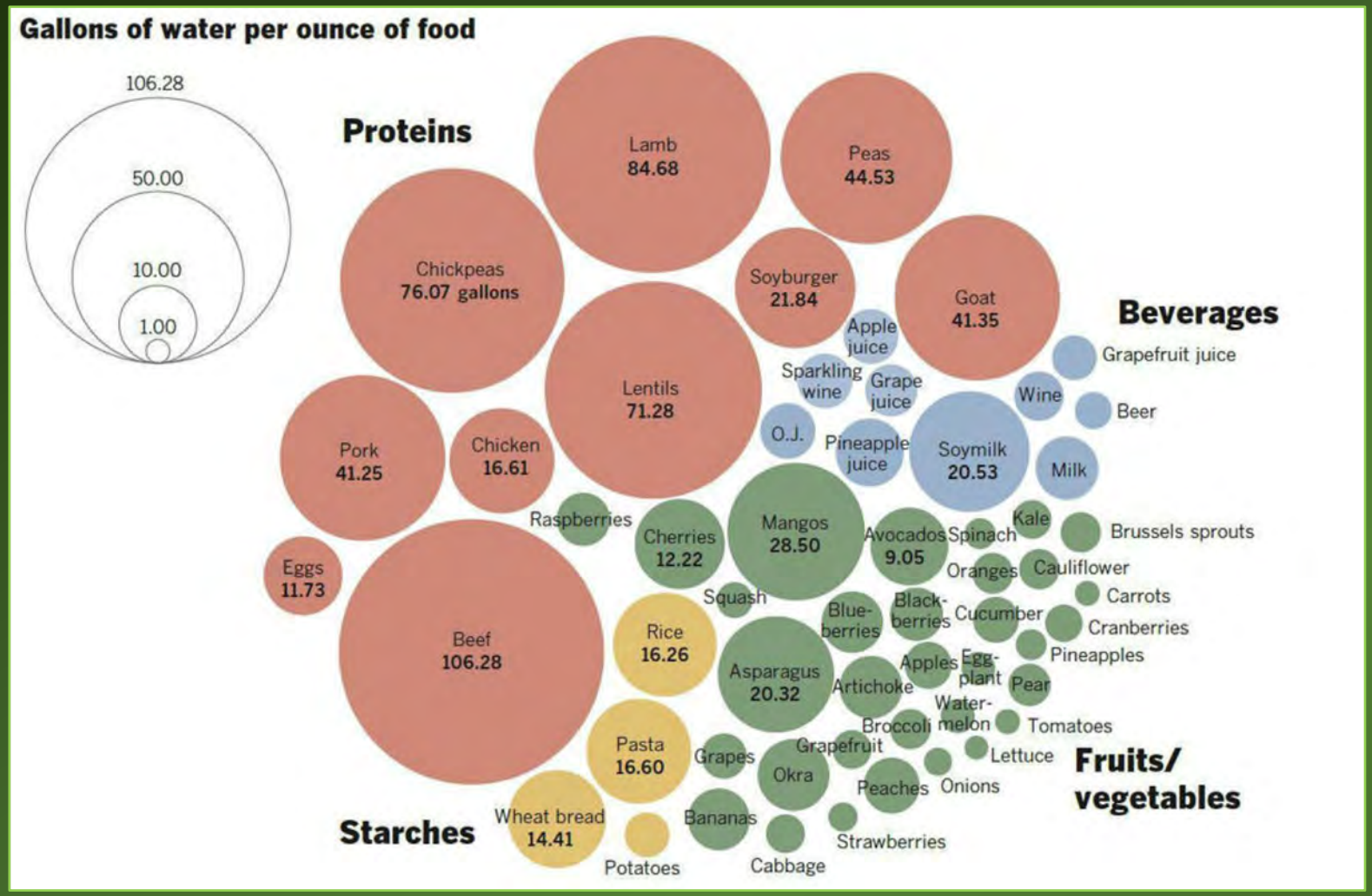
Don’t be a bystander in this slow moving disaster

Help people see we can win

We have to solve it with our primate brain

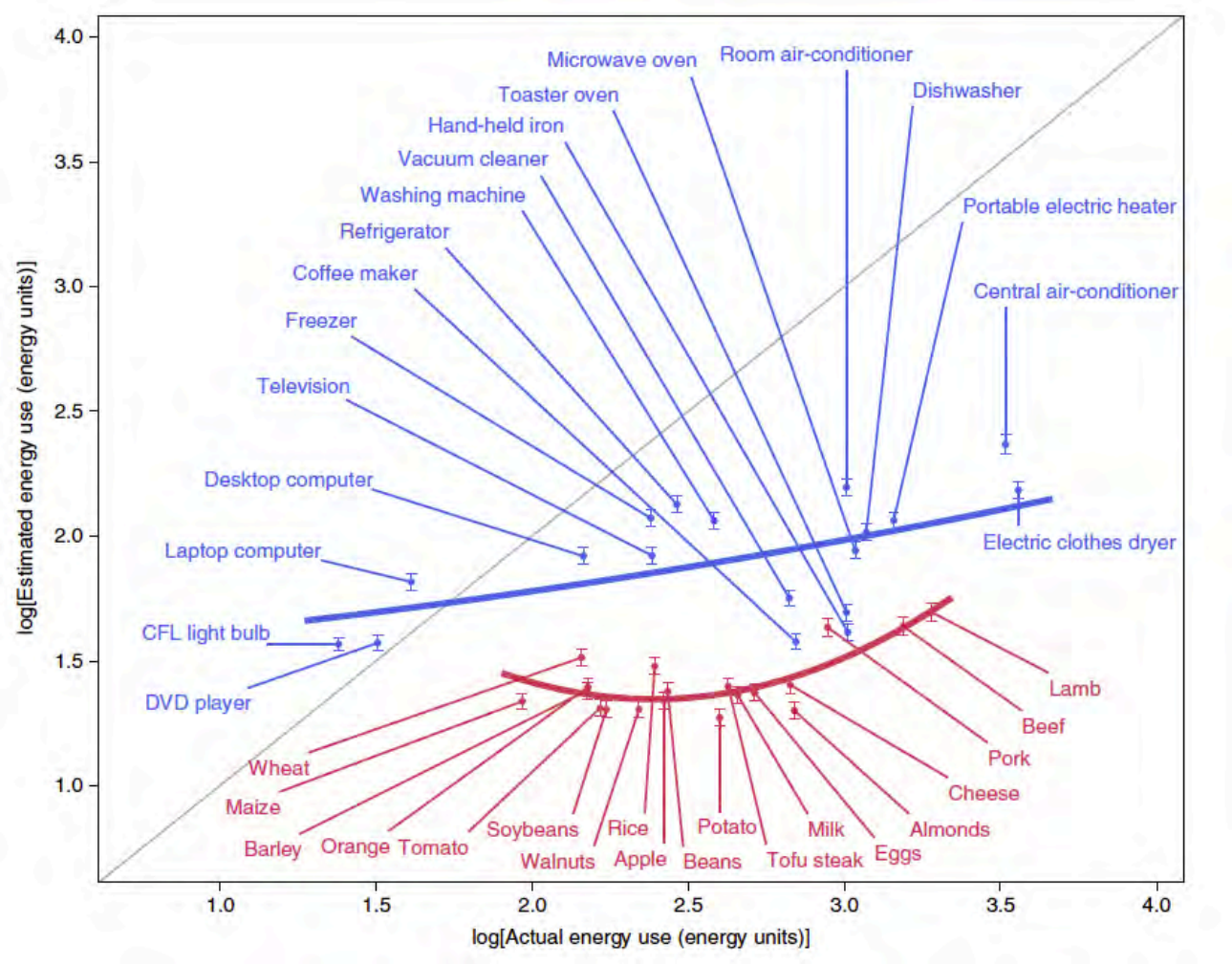
If we can repair the Ozone hole we can mitigate climate change

Know the Impact of your Dinner Plate



A.R. Camilleri: Nature Climate Change 2019

Known Our Blind Spots When you Shop



A.R. Camilleri: Nature Climate Change 2019

Don’t make Godzilla the Town Planner

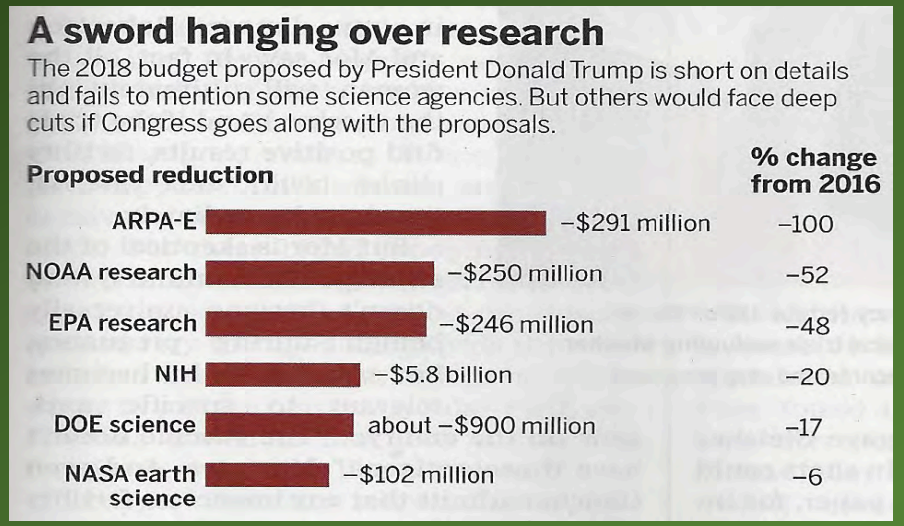
The NEW ENGLAND JOURNAL of MEDICINE

MEDICINE AND SOCIETY

Debra Malina, Ph.D., *Editor*

The Trump Administration and the Environment — Heed the Science

Jonathan M. Samet, M.D., Thomas A. Burke, Ph.D., M.P.H., and Bernard D. Goldstein, M.D.



Air pollution science under siege at US environment agency

Nature, March 2019

October 2018, the agency also dismantled a scientific advisory panel that works in parallel with the agency’s Clean Air Scientific Advisory Committee (CASAC), which advises officials on air-quality standards.

nature climate change

ARTICLES

https://doi.org/10.1038/s41558-020-00930-6

Check for updates

Right-wing ideology reduces the effects of education on climate change beliefs in more developed countries

Gabriela Czarnek, Małgorzata Kossowska and Paulina Szwed

Persuasive Words are not Enough:

Holden Thorpe Science June 2020

- Future is grim
- Solutions are clear
- Let the healing begin
- Be your local Spokes person for your hospitals and community
- Scientific community is losing the battel against misinformation
- American Petroleum Industry has stood against progress

Flooding in Jakarta, Indonesia, February 2017. Source: World Meteorological Organization / Flickr

CDC Recommendations & Resources for Physicians Response to Climate Change

1. Anticipating climate impacts and assessing vulnerabilities
2. Projecting the disease burden
3. Assessing public health interventions
4. Developing and implementing a climate and health adaptation plan
5. Evaluating impacts and improving the quality of activities

Resource	Website	Description
American College of Physicians	www.acponline.org	Climate change tool kit
American Lung Association	www.lung.org	"State of the Air" report on air pollution
Health Care without Harm	https://noharm.org	Environmentally responsible health care, physician advocacy network
Medical Society Consortium on Climate and Health	https://medsocietiesforclimatehealth.org	Coalition of U.S. medical societies supporting climate action, educational materials, and consensus statements
Physicians for Social Responsibility	www.psr.org	List of local chapters, "Climate change makes me sick" educational campaign
The Lancet Countdown on Health and Climate Change	www.lancetcountdown.org	International research collaboration tracking the world's response to climate change, including a policy brief for the United States

All UC Campus to Become Carbon Neutral by 2025

When you are out to Describe the Truth

James Hansen, who gave a climate warning in 1988 Senate testimony, says real hoax is by leaders claiming to take action

Leave elegance to the Tailor

Bring forward what is true, Write it so that it is clear, Defend it to your last breath

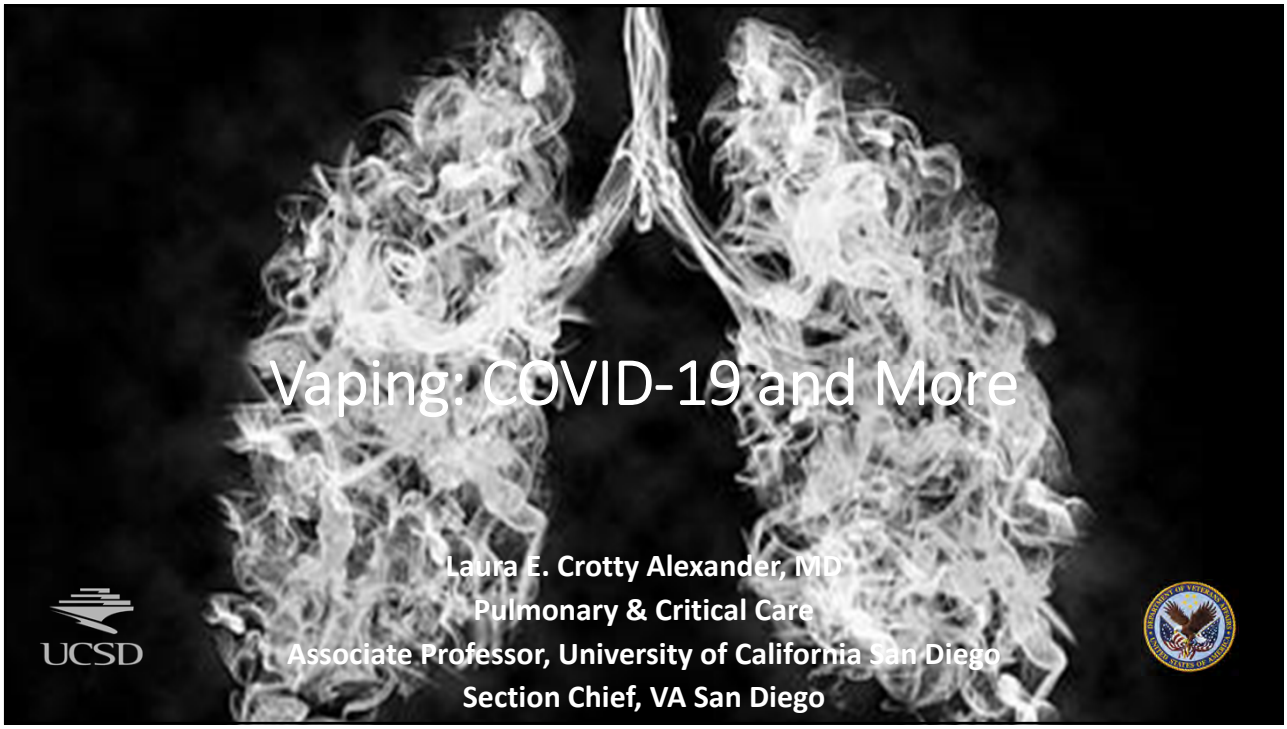
Ludwig Boltzmann

Vaping: COVID-19 and More

3:50 p.m. – 4:35 p.m.

LAURA CROTTY ALEXANDER, MD
UC SAN DIEGO

Dr. Laura Crotty Alexander received her medical degree from Duke University. She did her residency in Internal Medicine at Massachusetts General Hospital and fellowship in Pulmonary and Critical Care Medicine (PCCM) at Harvard. Currently, she is the section chief for PCCM at the VA San Diego Healthcare System and is an Associate Professor at UCSD. Her research focuses on the health effects of e-cigarettes and vaping, and is funded by the NIH, VA and TRDRP.



1

Disclosures

Funding
NIH NHLBI K24, PI Crotty Alexander
VA Merit, PI Crotty Alexander
TRDRP SVFSI, PI Crotty Alexander
NIH NHLBI R01, PI Castaldi

2

Where to start?

3

4

Gateway Effect

OR 3.5 for subsequent smoking initiation

June 26, 2017

Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults

A Systematic Review and Meta-analysis

Samir Soneji, PhD[1,2]; Jessica L. Barrington-Trimis, PhD[3]; Thomas A. Wills, PhD[4]; et al

JAMA Pediatr.

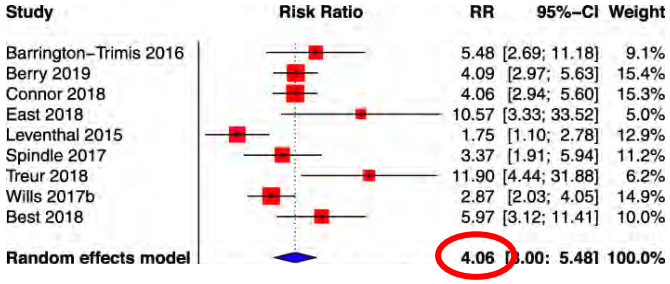
5

Gateway Effect to Conventional Smoking

Published: 03 June 2021

Association between electronic cigarette use and tobacco cigarette smoking initiation in adolescents: a systematic review and meta-analysis

Doireann O'Brien, Jean Long ✉, Joan Quigley, Caitriona Lee, Anne McCarthy & Paul Kavanagh



6

Vaping e-cigarettes increases the odds that you will initiate smoking conventional tobacco.

7

Newer generation e-cigarettes
+
Intent to quit

E-cigs may help smokers achieve cessation from conventional tobacco….

8

Harm reduction?

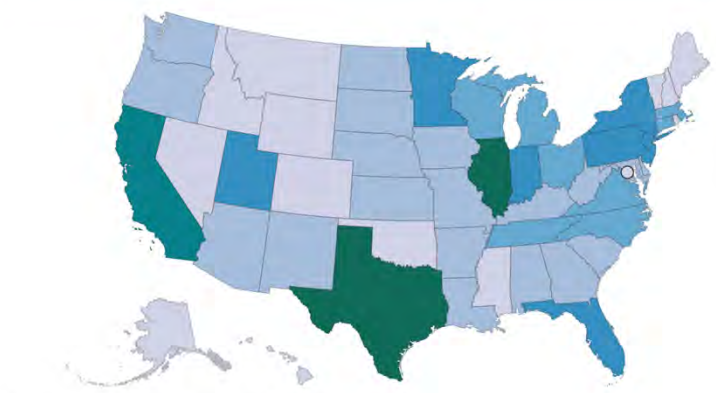
9

Summer-Winter 2019

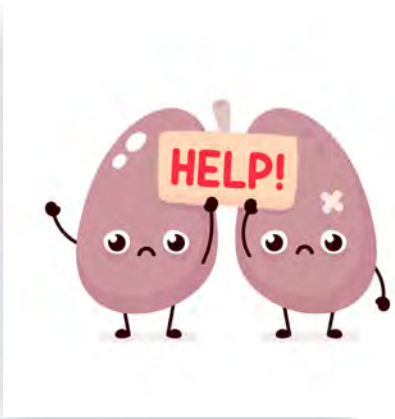
E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI)

10

Number of Hospitalized EVALI Cases or Deaths Reported to CDC as of January 14, 2020



Territories AS GU MH FM PW PR VI



11

Symptoms

1. Respiratory
2. Gastrointestinal
3. Systemic

- Shortness of breath, cough, chest pain

- Abdominal pain, nausea, vomiting, diarrhea

- Fatigue, fever, weight loss

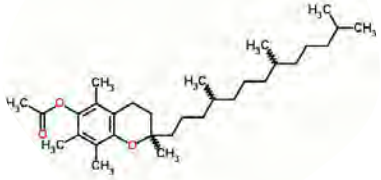
12

<u>Disease of the young</u>
Median age of 22 (13 to 71)
79% under 35

82% use THC

13

Vitamin E acetate



14

American Journal of Respiratory and Critical Care Medicine

E-Cigarette or Vaping Product Use–associated Lung Injury: Developing a Research Agenda. An NIH Workshop Report

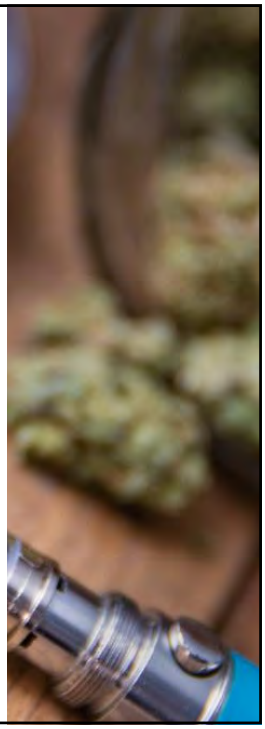
Laura E. Crotty Alexander [1,2], Lorraine B. Ware [3,4], Carolyn S. Calfee [5], Sean J. Callahan [6,7], Thomas Eissenberg [8,9], Carol Farver [10], Maciej L. Goniewicz [11], Ilona Jaspers [12], Farrah Kheradmand [13,14], Talmadge E. King , Jr.[5], Show

1. Evaluating puff topography, breath holding or bearing down via questionnaires, interviews and assessment of vaping techniques in the laboratory setting may clarify the role of vaping styles in disease pathogenesis.
2. Generation of more specific criteria for the diagnosis of EVALI is needed to differentiate between EVALI and other lung diseases caused by vaping. ★
3. A definition of disease severity may help guide clinical research studies of EVALI, such as an O_2 requirement of ≥ 6 L/minute for severe, 1-5 L/minute for moderate, and no O_2 requirement in mild cases.
4. Classification of both duration of symptoms and disease severity may help identify risk factors for different severities and uncover whether different disease presentations represent a continuum of one disease or represent variants of the disease.
5. Conducting translational research studies on biospecimens obtained from EVALI subjects, across different timepoints and severities of disease, to define the cell types, phenotypes and molecular pathways involved may yield critical data regarding mechanisms of injury and inflammation.
6. Developing an EVALI animal model would give insight into disease mechanisms and allow for rapid testing of potential therapeutic agents.
7. Research is needed related to addiction relapse prevention.
8. Longitudinal studies in confirmed cases to define the mortality, and short- and long-term morbidity for these patients is an important research need. ★

EVALI-19
or
EVALI-VEA

15

Vaping THC / CBD e-liquids is dangerous because it could contain Vitamin E acetate, which causes EVALI



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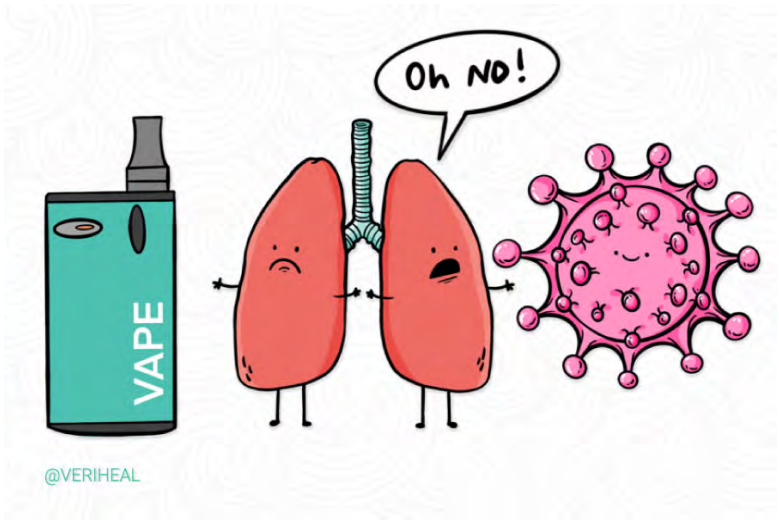
2020



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JAMA Network

From: **Association of Smoking and Cumulative Pack-Year Exposure With COVID-19 Outcomes in the Cleveland Clinic COVID-19 Registry**

JAMA Intern Med. 2021;181(5):709-711

Table 2. Logistic Regression Models for COVID-19 Outcomes by Smoking

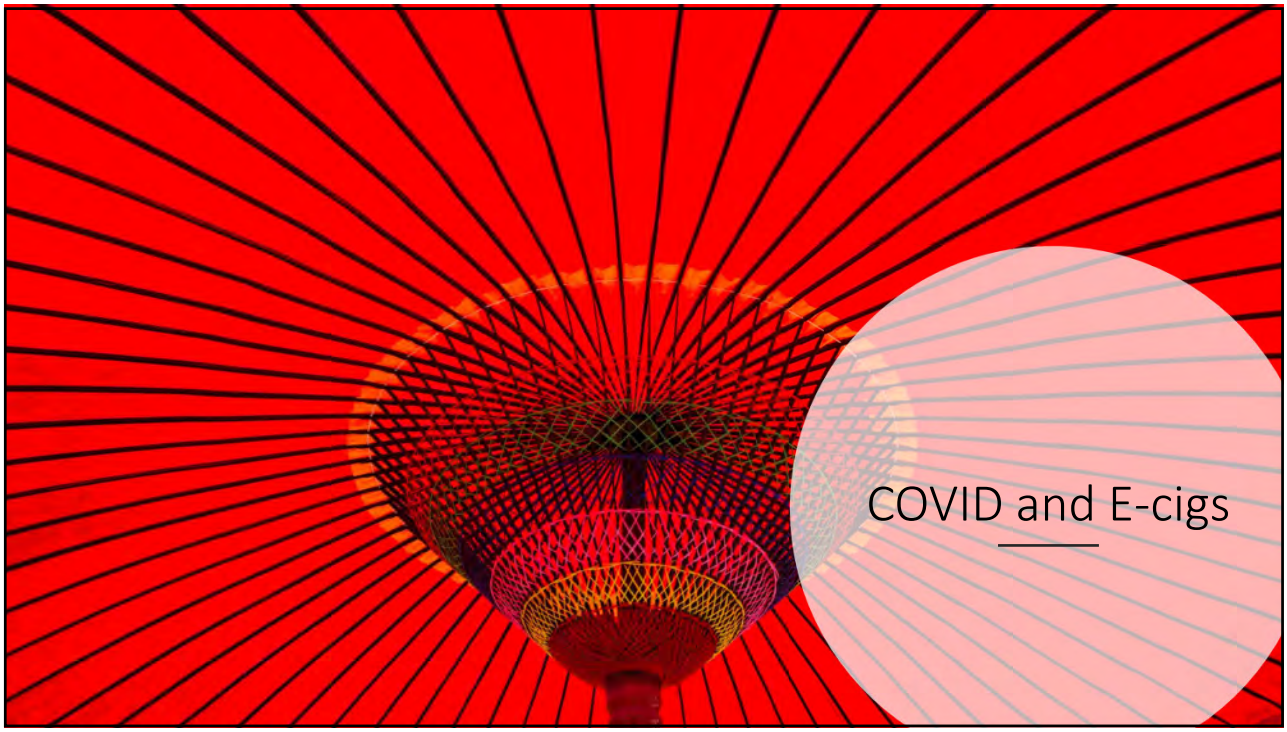
Outcome	Odds ratio (95% CI) Unadjusted	Adjusted for age, race, and gender
Hospitalization given a positive COVID-19 test		
Never smoker	1 [Reference]	1 [Reference]
0-10 Pack-years	1.41 (1.10-1.81)	0.99 (0.76-1.30)
10-30 Pack-years	2.48 (2.01-3.07)	1.41 (1.12-1.78)
>30 Pack-years	4.65 (3.72-5.82)	2.25 (1.76-2.88)
ICU admission given a positive COVID-19 test and hospitalization		
Never smoker	1 [Reference]	1 [Reference]
0-10 Pack-years	1.33 (0.84-2.08)	1.19 (0.75-1.89)
10-30 Pack-years	1.74 (1.23-2.45)	1.55 (1.09-2.21)
>30 Pack-years	2.11 (1.54-2.89)	1.69 (1.23-2.35)
Death given a positive COVID-19 test		
Never smoker	1 [Reference]	1 [Reference]
0-10 Pack-years	2.38 (1.50-3.80)	1.66 (0.98-2.83)
10-30 Pack-years	3.40 (2.31-5.02)	1.47 (0.96-2.27)
>30 Pack-years	6.11 (4.33-8.61)	1.89 (1.29-2.76)

18

Conventional Tobacco

1. Smoking is correlated with higher rates of SARS-CoV-2 infection
2. Smoking increases severity of COVID-19
3. Smoking increases mortality in COVID-19

19



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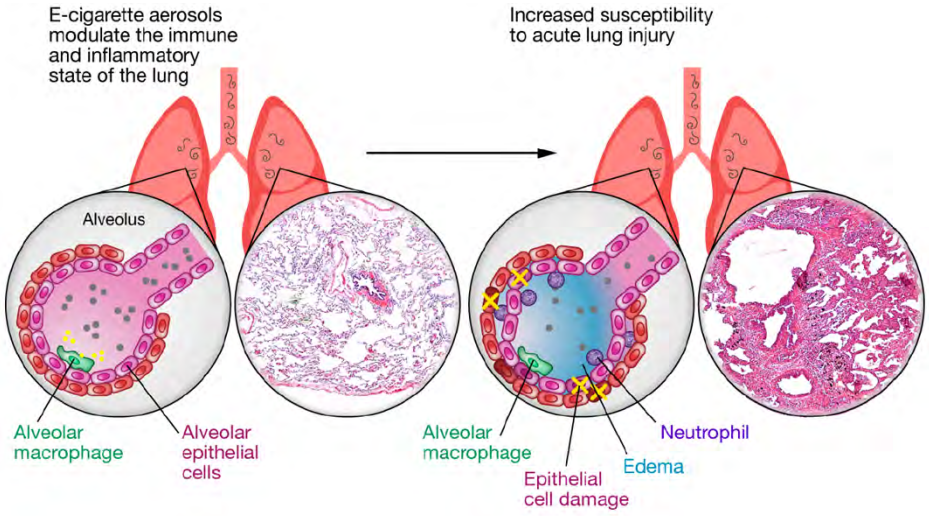
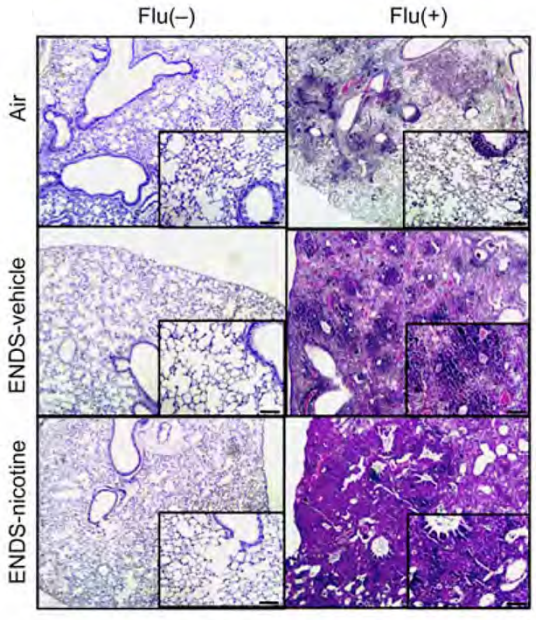


Crotty Alexander et al, JCI 2020

21

Mouse Data:
Increased susceptibility to influenza



Madison et al, JCI 2019

22

Vaping is likely to increase some of the inflammation occurring in COVID-19

23

JOURNAL OF ADOLESCENT HEALTH
Improving the Lives of Adolescents and Young Adults
SAHM

2020

	EVER-use	Past 30d use
	COVID-19–positive diagnosis (n = 4,048)	COVID-19–positive diagnosis (n = 4,048)
	Odds ratio (95% CI)	Odds ratio (95% CI)
Inhaled tobacco products		
Cigarettes only	2.32 (.34, 15.86)	1.53 (.29, 8.14)
E-cigarettes only	**5.05 (1.82, 13.96)** ★	1.91 (.77, 4.73)
Dual use	**6.97 (1.98, 24.55)** ★	**6.84 (2.40, 19.55)** ★

24

2020

Vaping linked to COVID-19 risk in teens and young adults

Data collected in May shows that teenagers and young adults who vape face a much higher risk of COVID-19 than their peers who do not vape, Stanford researchers found.

August 11, 2020 - By Erin Digitale

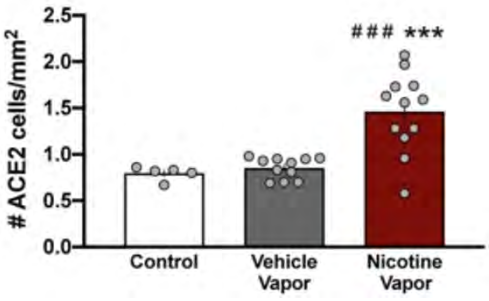
25

2021

Environmental Toxicology and Pharmacology
Volume 86, August 2021, 103656

E-cigarette vape and lung ACE2 expression: Implications for coronavirus vulnerability

Valeria Lallai [1], Letizia Manca [1], Christie D. Fowler



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MAYO CLINIC News Network

2022

By Jay Furst

E-cigarette users who test positive for COVID-19 are more likely to experience COVID-19 symptoms

January 13, 2022

27

28

MDPI

2021

Cigarette and E-Cigarettes Dual Users, Exclusive Users and COVID-19: Findings from Four UK Birth Cohort Studies

by Daniel Tzu-Hsuan Chen * and Christina N. Kyriakos

Dual use was associated with 2.15-fold higher odds of COVID-19 infection

29

> Am J Health Promot. 2022 Mar;36(3):421-428.

2022

Assessment of Exclusive, Dual, and Polytobacco E-Cigarette Use and COVID-19 Outcomes Among College Students

Ashley L Merianos

Poly-tobacco and Dual use leads to higher symptomatology in COVID-19

30

> Addict Behav. 2022 Mar

2022

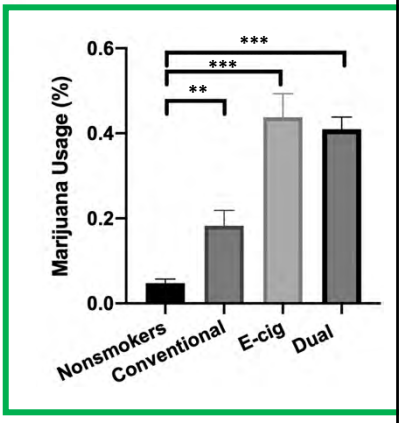
Concurrent use of e-cigarettes and cannabis and associated COVID-19 symptoms, testing, and diagnosis among student e-cigarette users at four U.S. Universities

Ashley L Merianos

52% of e-cig users also use cannabis

E-cigarette + MJ users were:

- 3.53x more likely to have COVID-19 symptoms
- 1.85x more likely to test positive



Advani et al., March 2022

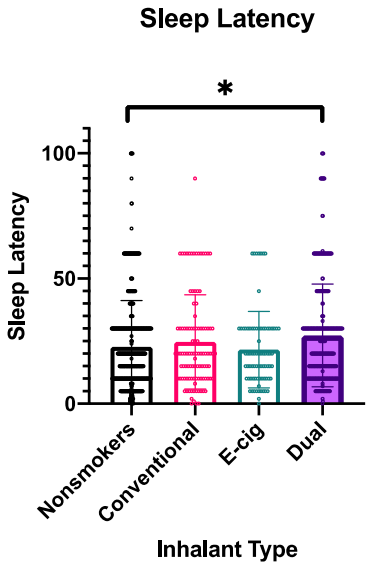
31

Does e-cigarette use increase risk of COVID-19?

Unclear, but Dual Use with conventional tobacco or marijuana does!

32

Side Notes on Sleep



N = 933

Advani et al. accepted 3/2022

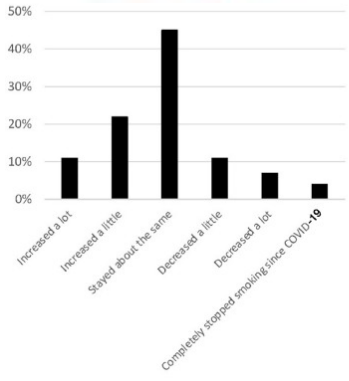
33

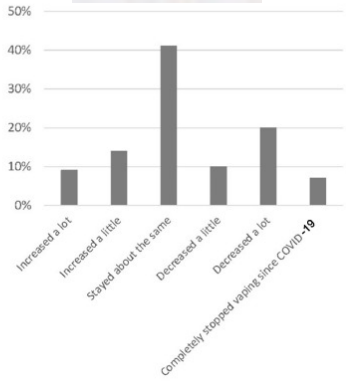
2022

> Am J Prev Med. 2022 Mar

Smoking and E-Cigarette Use Among U.S. Adults During the COVID-19 Pandemic

Sara M Kalkhoran





34

Does vaping cause cancer?

35

LUNG CANCER

REVIEW | VOLUME 153, P11-20, MARCH 01, 2021

Vaping and lung cancer – A review of current data and recommendations

Dara Bracken-Clarke • Dhruv Kapoor • Anne Marie Baird • ... Kathy Gately • Sinead Cuffe • Stephen P. Finn • Show all authors

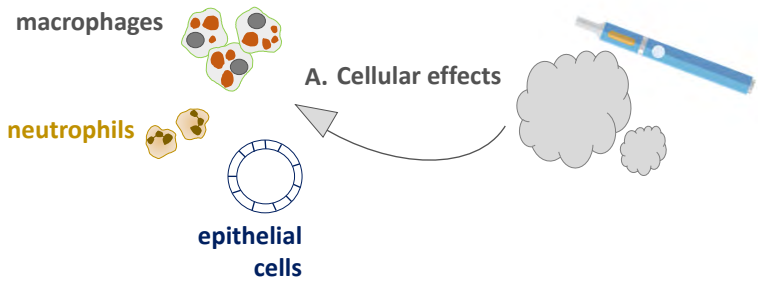
Although research remains somewhat equivocal, **there is clear reason for concern regarding the potential oncogenicity of E-Cigarettes/E-Liquids with a strong basic and molecular science basis**.

36

Does vaping cause cancer?

Probably!

37



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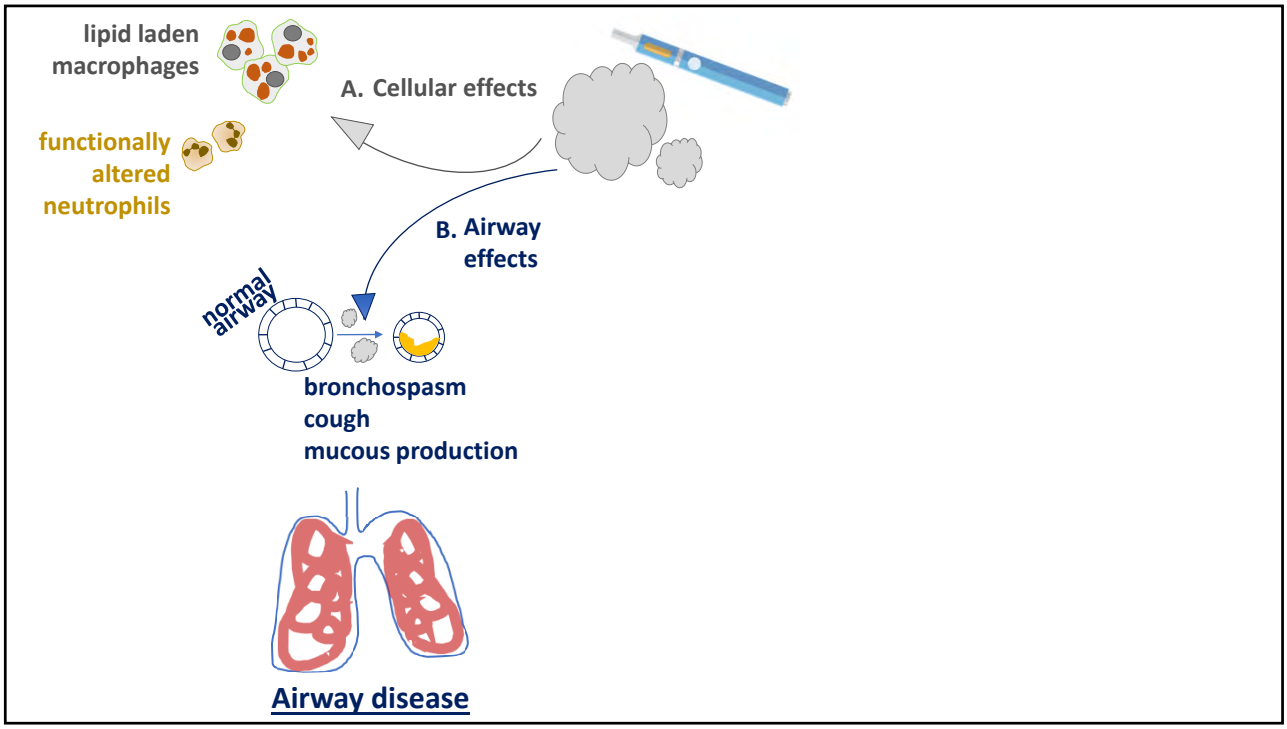
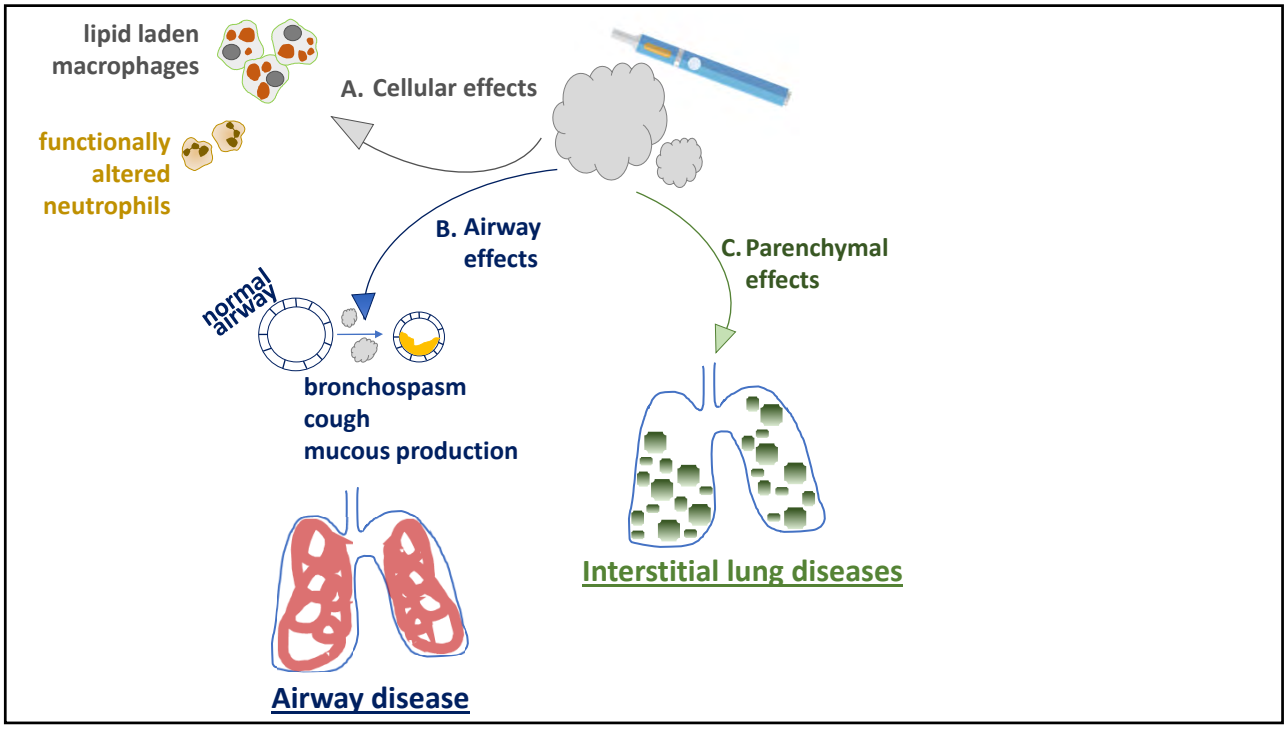
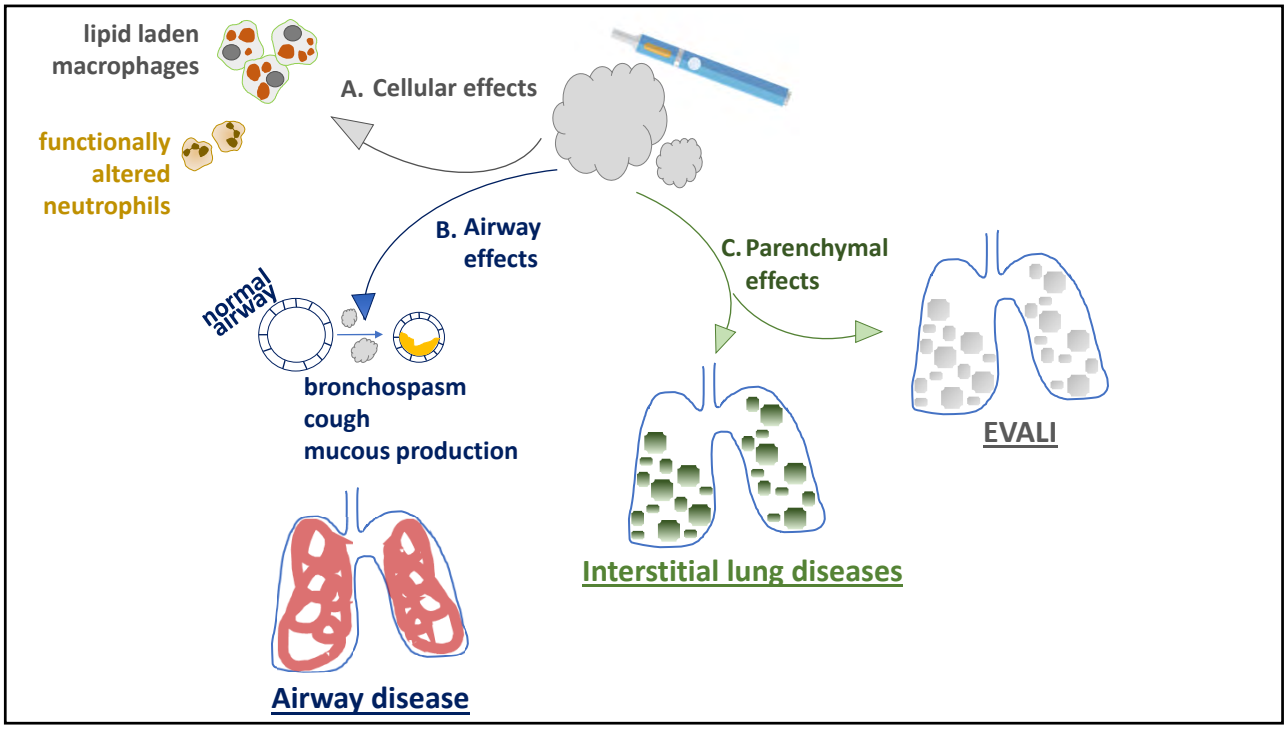

lipid laden macrophages
functionally altered neutrophils
A. Cellular effects
B. Airway effects
normal airway
bronchospasm
cough
mucous production
Airway disease

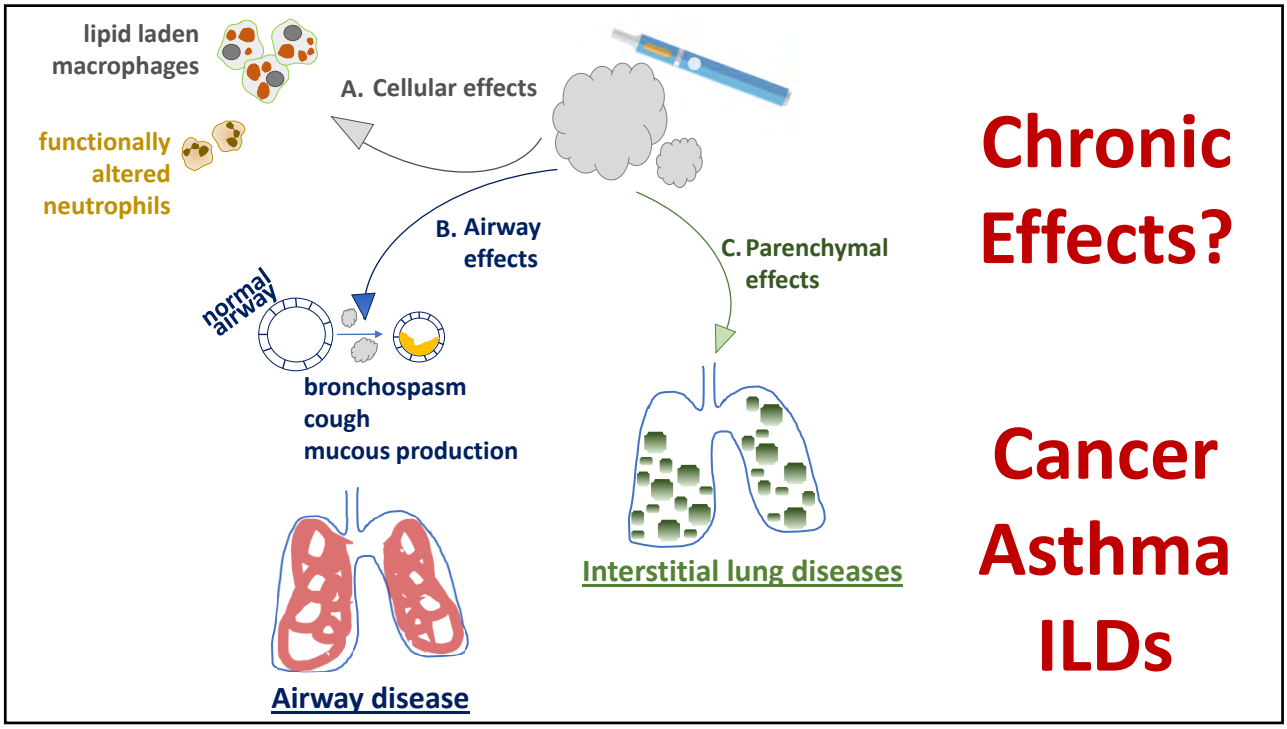
39


lipid laden macrophages
functionally altered neutrophils
A. Cellular effects
B. Airway effects
C. Parenchymal effects
normal airway
bronchospasm
cough
mucous production
Airway disease
Interstitial lung diseases

40


lipid laden macrophages
functionally altered neutrophils
A. Cellular effects
B. Airway effects
C. Parenchymal effects
normal airway
bronchospasm
cough
mucous production
EVALI
Interstitial lung diseases
Airway disease

41


lipid laden macrophages
functionally altered neutrophils
A. Cellular effects
B. Airway effects
C. Parenchymal effects
normal airway
bronchospasm
cough
mucous production
Interstitial lung diseases
Airway disease
Chronic Effects?
Cancer
Asthma
ILDs

42

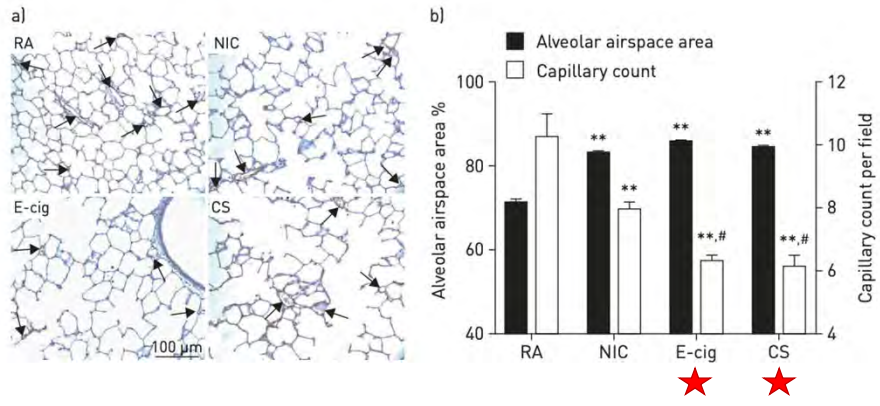
Emphysema?

43

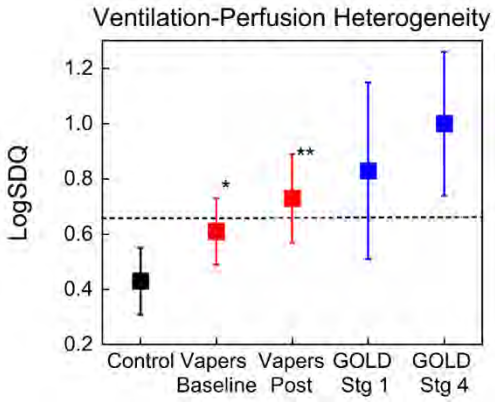
EUROPEAN RESPIRATORY *journal*

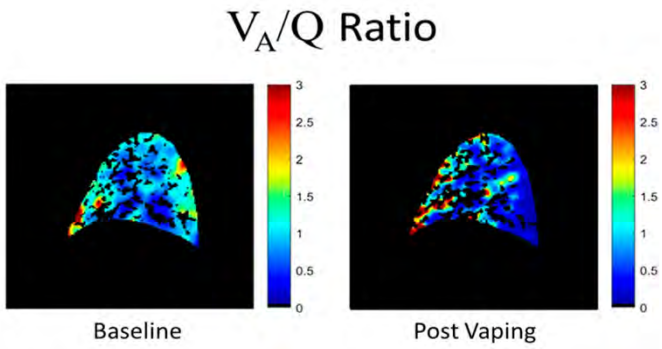
Viktorija Reinikovaite[1], Ivan E. Rodriguez[2], Vijaya Karoor[1], Aline Rau[2], Becky B. Trinh[2], Frederic W-B. Deleyiannis[2] and Laima Taraseviciene-Stewart[1]

The effects of electronic cigarette vapour on the lung: direct comparison to tobacco smoke



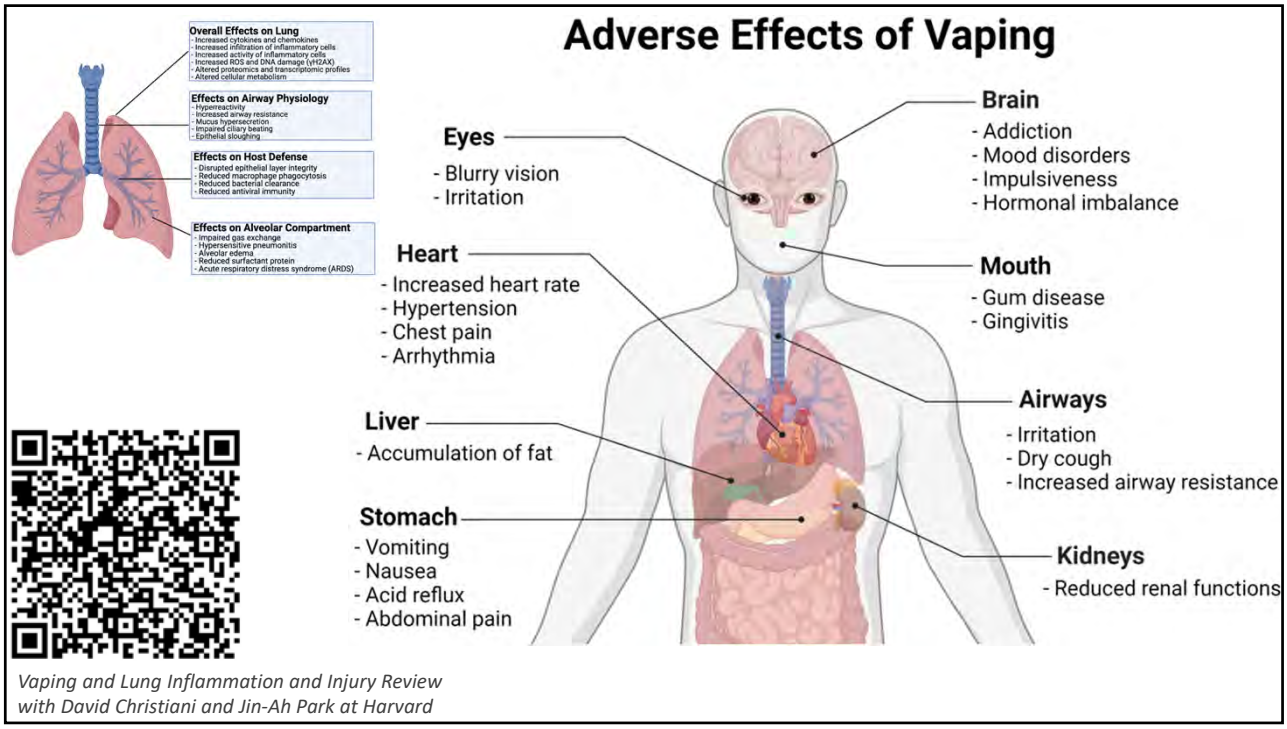
44





Abhilash S. Kizhakke Puliyakote et al. JAP 2021

45



Vaping and Lung Inflammation and Injury Review with David Christiani and Jin-Ah Park at Harvard

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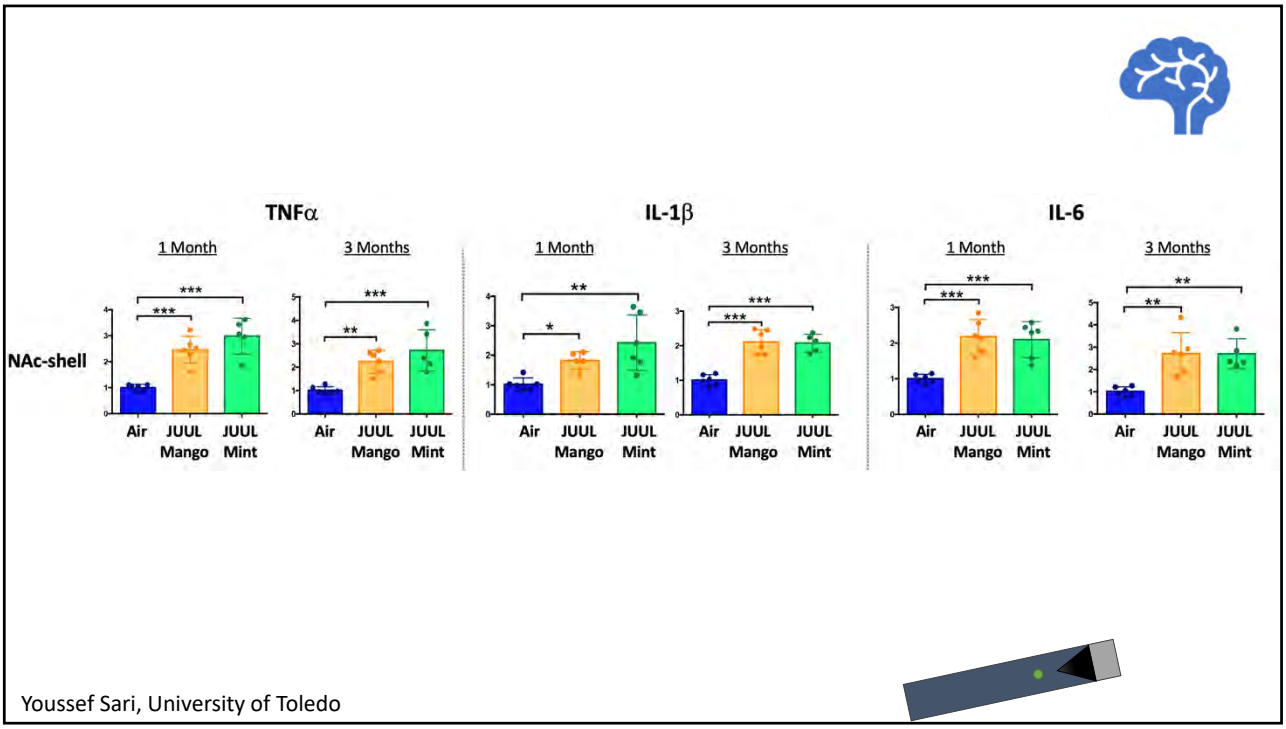
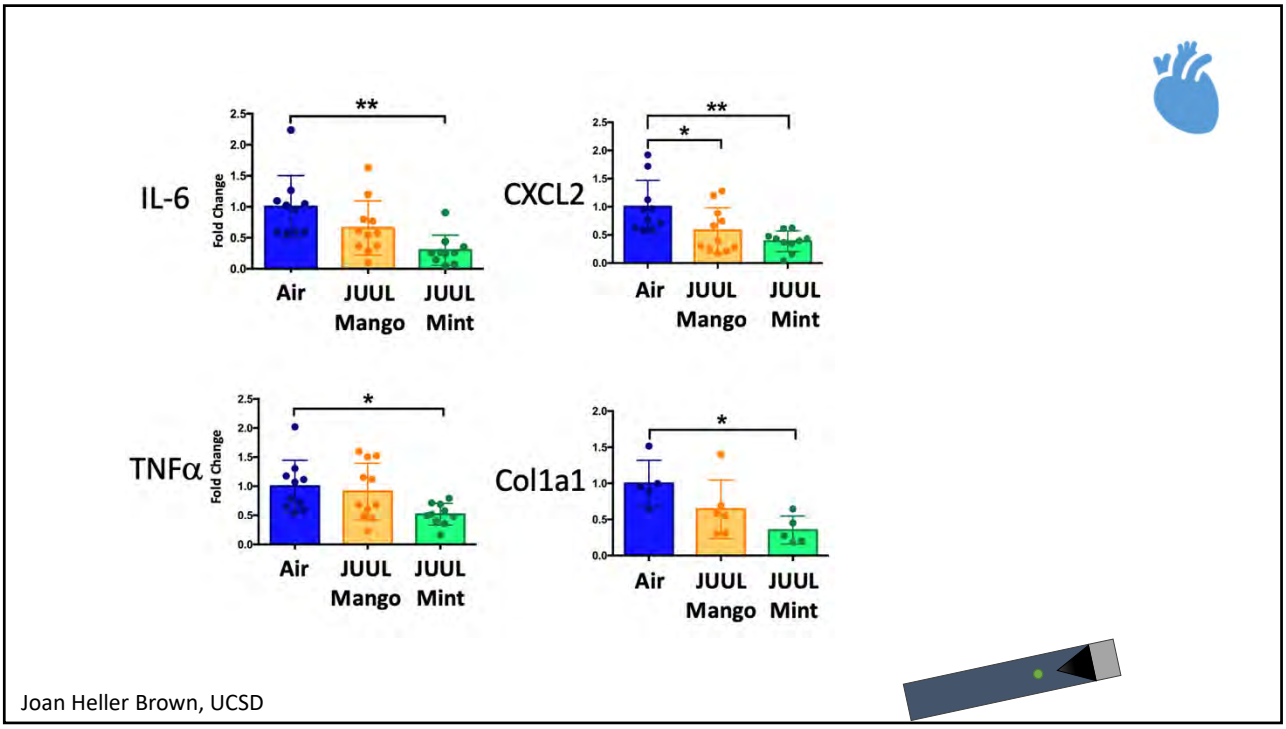


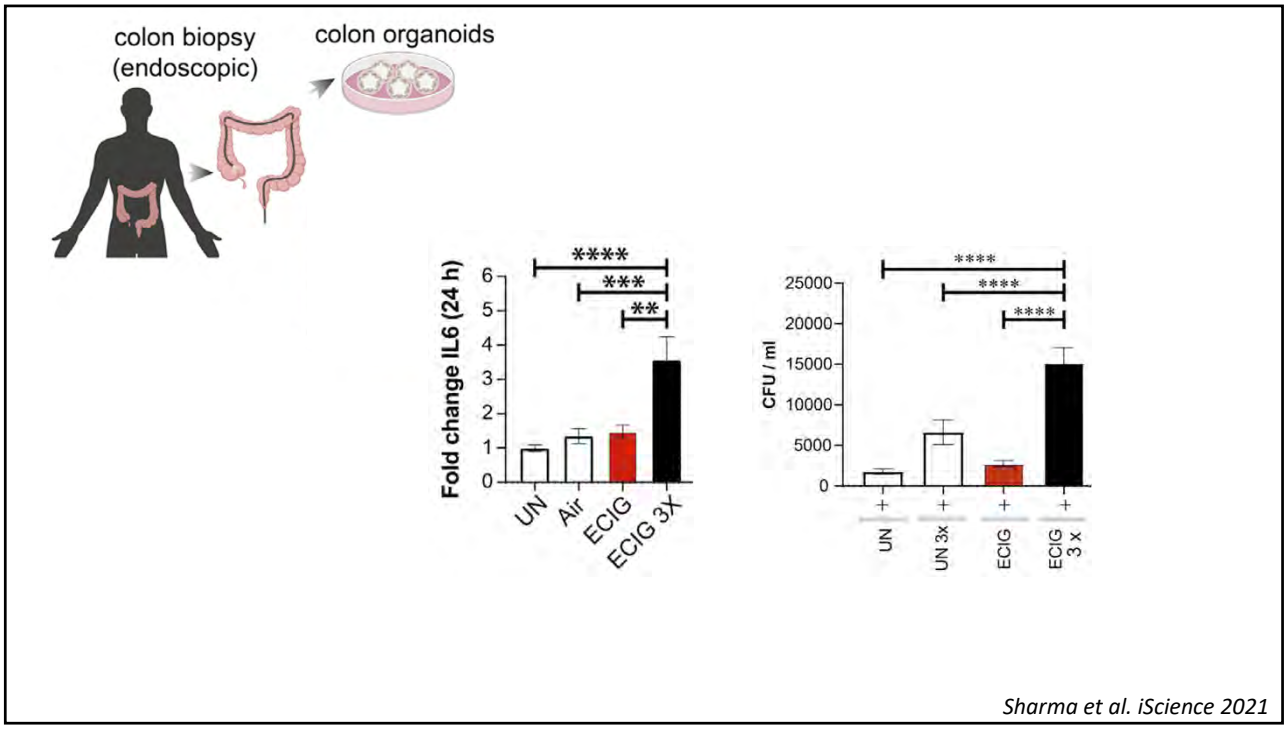
Youssef Sari, University of Toledo

47



Joan Heller Brown, UCSD

48



Sharma et al. iScience 2021

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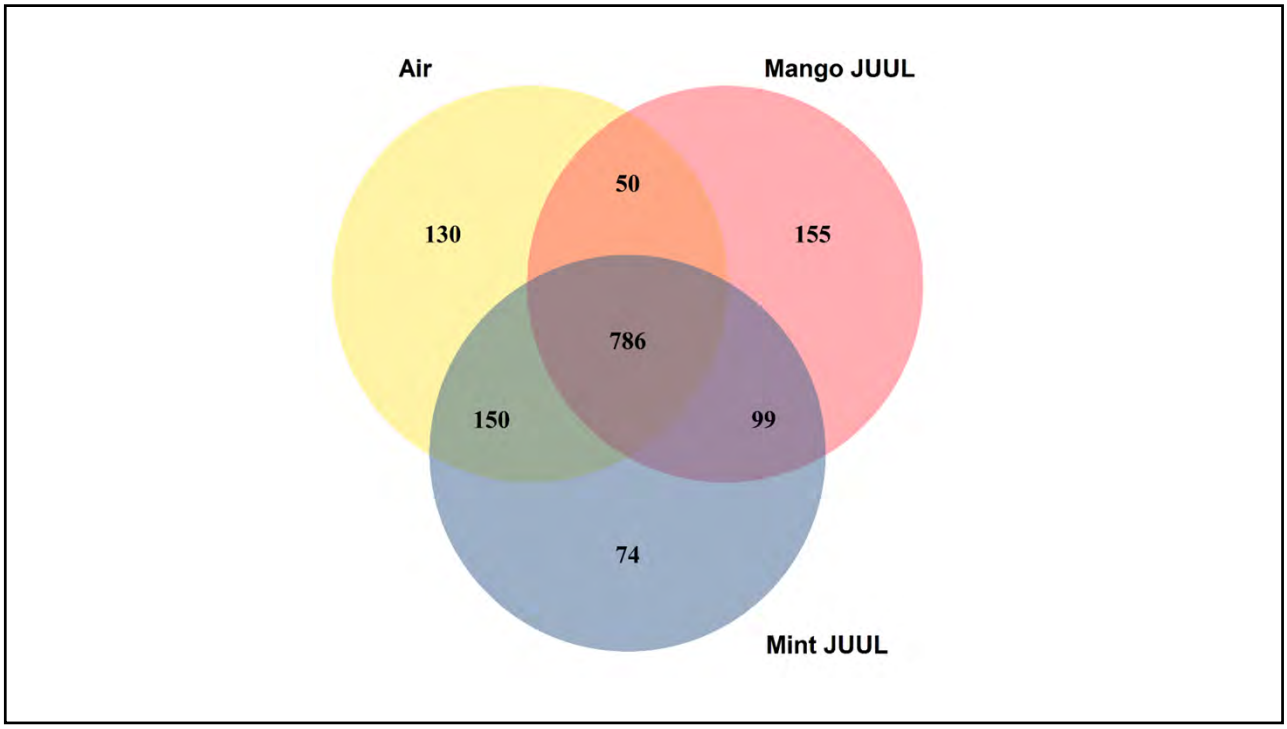

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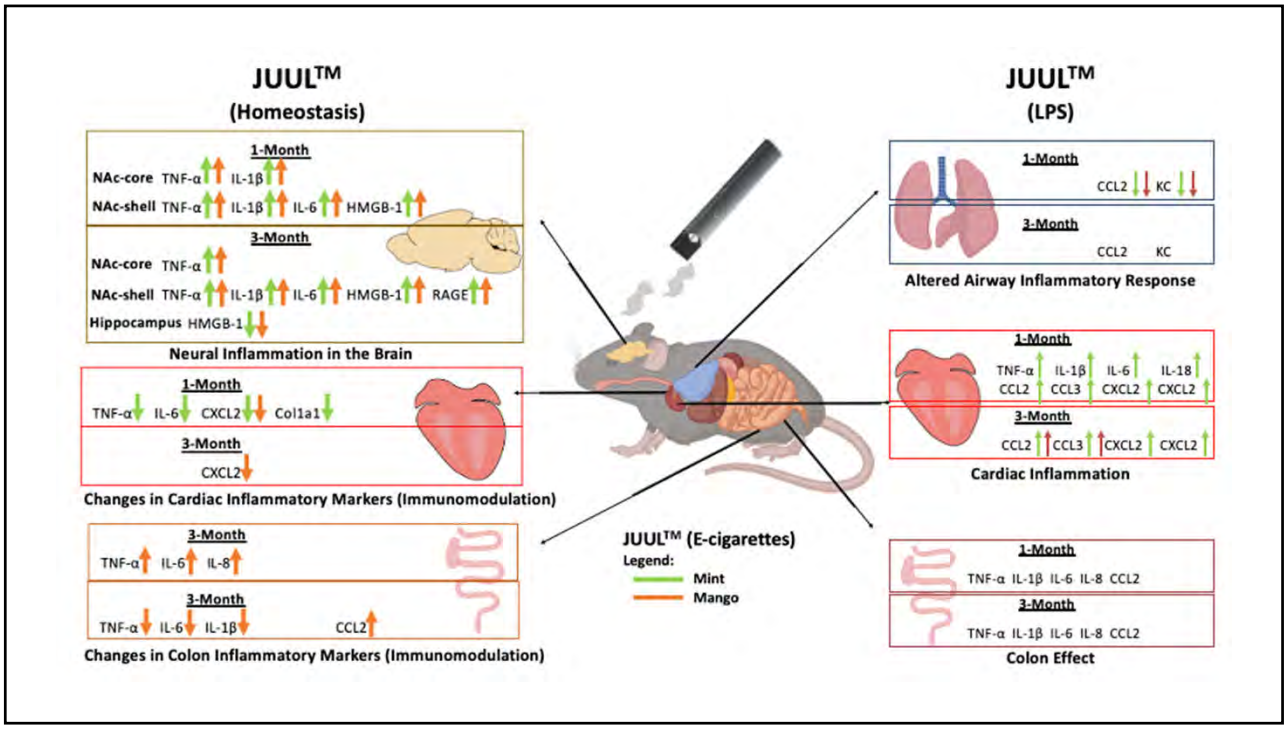
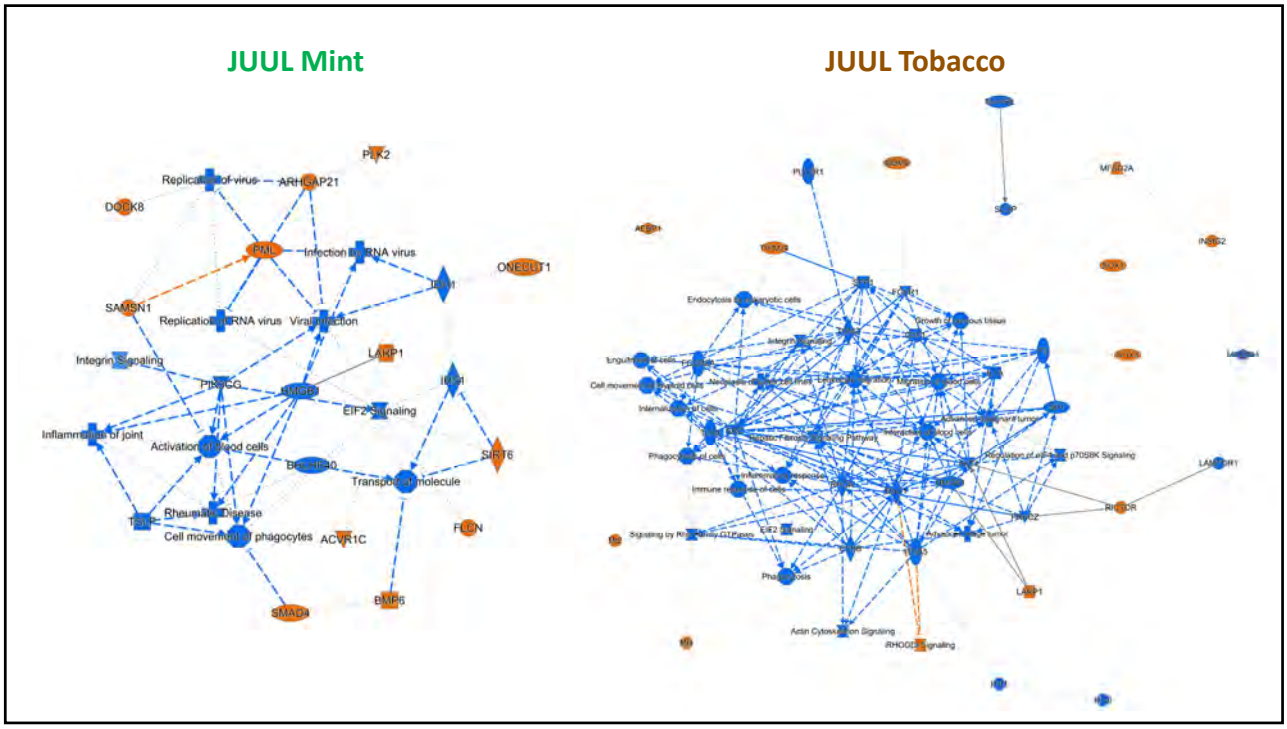

JUUL™
(Homeostasis)
1-Month
NAc-core TNF-α IL-1β
NAc-shell TNF-α IL-1β IL-6 HMGB-1
3-Month
NAc-core TNF-α
NAc-shell TNF-α IL-1β IL-6 HMGB-1 RAGE
Hippocampus HMGB-1
Neural Inflammation in the Brain
1-Month
TNF-α IL-6 CXCL2 Col1a1
3-Month
CXCL2
Changes in Cardiac Inflammatory Markers (Immunomodulation)
3-Month
TNF-α IL-6 IL-8
3-Month
TNF-α IL-6 IL-1β CCL2
Changes in Colon Inflammatory Markers (Immunomodulation)
JUUL™ (E-cigarettes)
Legend:
Mint
Mango
JUUL™
(LPS)
1-Month
CCL2 KC
3-Month
CCL2 KC
Altered Airway Inflammatory Response
1-Month
TNF-α IL-1β IL-6 IL-18
CCL2 CCL3 CXCL2 CXCL2
3-Month
CCL2 CCL3 CXCL2 CXCL2
Cardiac Inflammation
1-Month
TNF-α IL-1β IL-6 IL-8 CCL2
3-Month
TNF-α IL-1β IL-6 IL-8 CCL2
Colon Effect

51


JUUL Mint
JUUL Tobacco
PLK2
Replication of virus
ARHGAP21
DCTK8
PML
Infection by RNA virus
ONECUT1
IRF1
SAMSN1
Replication of RNA virus
Viral Infection
Integrin Signaling
LAIR1
PIK3CG
HMGB1
IRF3
EIF2 Signaling
Inflammation of joint
Activation of blood cells
SIRT6
Transport of molecule
Rheumatic Disease
Cell movement of phagocytes
ACVR1C
FLCN
SMAD4
BMP6

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Conclusions

- E-cigarettes increase odds of initiating conventional tobacco use
- E-cigarettes cause lung disease
- E-cigarettes are not great for smoking cessation (perpetuate nicotine addiction)
- E-cigarettes are highly likely to cause cancer
- E-cigarettes affect organ systems across the body

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Conclusions

- Secondhand exposure to e-cigarette aerosols is associated with increased respiratory symptoms and occurrence of asthma
- Dual use of e-cigarettes and conventional tobacco is the most concerning, with the greatest signals of toxicity – including COVID risk

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Collaborators
Xin Sun, UCSD Pediatrics
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Victor Nizet, UCSD Pediatrics
Atul Malhotra, UCSD
Joan Heller Brown, UCSD Pharmacy
Tatum Simonson, UCSD
David Pride, UCSD Pathology

David Christiani, Harvard
Jin-Ah Park, Harvard
Peter Castaldi, Harvard
Miranda Ween, Univ of Adelaide
Youssef Sari, Univ of Toledo
Sunit Singla, Univ of Illinois at Chicago
Elizabeth DiRenzo, Stanford
Peter Chen, Cedar Sinai

Thank you!

The Lab Crew
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Jarod Olay, BS MS
Ankita Mittal, MD
Shrey Patel, MD
Erica Lin, MD
Ana Lucia Fuentes, MD
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Jordan Marganski, BS
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William Merz
Sed Nilaad, BS MS
Niamh Malhotra
Ashley Du, BS
Arjun Patel, MD

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Funding
NIH NHLBI R01, PI Crotty Alexander
NIH NHLBI R01, PI Castaldi
VA Merit, PI Crotty Alexander
TRDRP, PI Crotty Alexander
TRDRP, PI Sun

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Metabolomics

Fibrosis

Human inflammation

NIH Workshop

58

Post-Test and Adjourn

4:35 p.m. – 4:45 p.m.

KRISTINA KUDELKO, MD
STANFORD UNIVERSITY

GAURAV SINGH, MD, MPH
VA PALO ALTO HEALTH CARE SYSTEM
STANFORD UNIVERSITY

Pandemic Career Development and Wellness Panel (NON-CME)

5:00 p.m. – 6:00 p.m.

Moderators:
Gaurav Singh, MD, MPH and Kristina Kudelko, MD
Panelists: Michelle Moore, MD; Susan Murin, MD, MSc, MBA; Mark Nicolls, MD; Dean Sheppard, MD
***Available to view live via Zoom link for non-attendees**

Women In Pulmonary, Critical Care, and Sleep Medicine (NON-CME)

6:30 p.m. – 8:00 p.m.

Moderator: Angela Wang, MD