IACFS/ME
2022 Conference Highlights

Lily Chu, MD, MSHS
iacfsmeorg@gmail.com
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Conference Overview

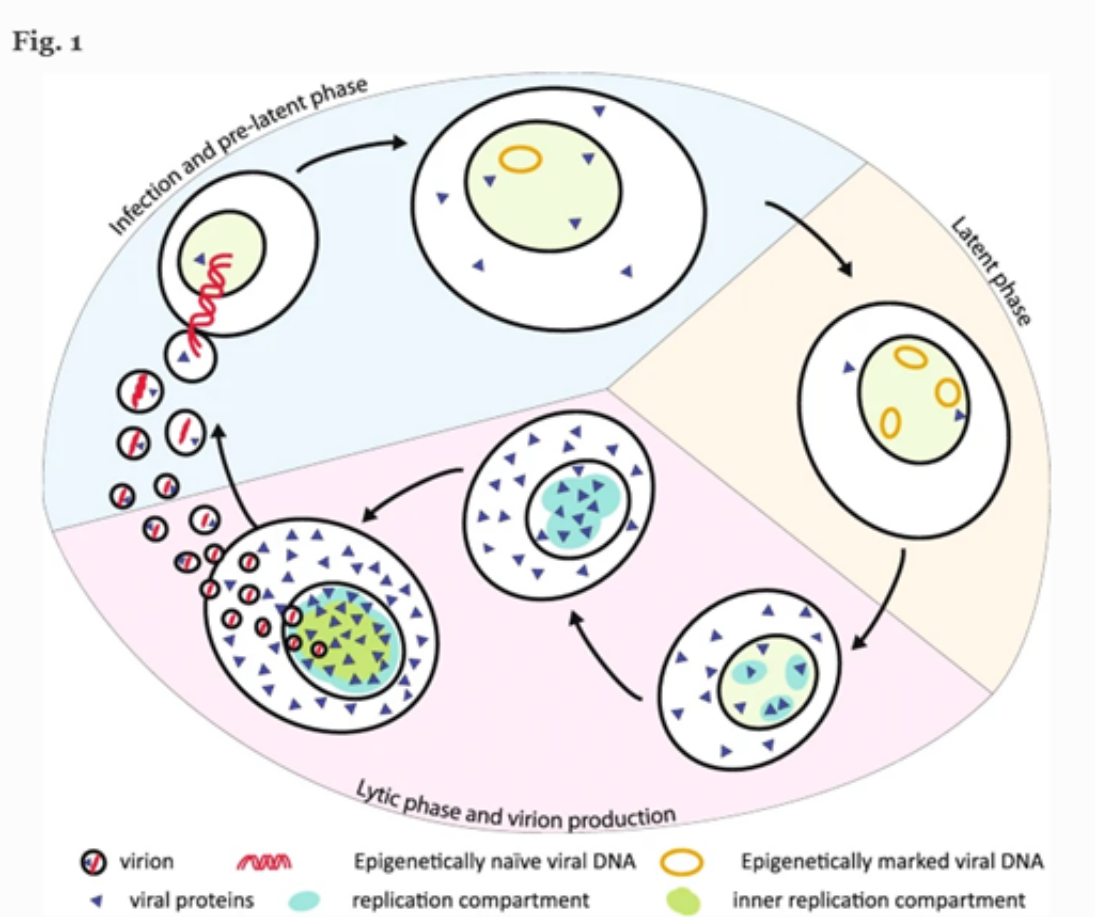
* 3.5 days, virtual
* 300+ attendees
* 58 speakers and 20+ posters
* 30% of attendees from outside US (Europe, Australia and Japan)
* 20% students, trainees, early career professionals

Three Themes & Questions

* Infection: EBV
* Immune exhaustion
* Imbalance in autonomic nervous system

* What is the context for this study?
* What question/ issue is it trying to address?
* How might results advance understanding or affect care?

Infection: EBV life cycle



Current tests & antivirals target these phases

BUT what if this picture is wrong?

May explain “normal” tests & ineffective treatments

From: https://link.springer.com/article/10.1007/s00281-020-00792-2

Infection: EBV abortive lytic state

Cox, Brandon S., et al. "EBV/HHV-6A DUTPases Contribute to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Pathophysiology by Enhancing T_{FH} Cell Differentiation and Extrafollicular Activities." *JCI Insight*, vol. 7, no. 11, June 2022. *insight.jci.org*, https://doi.org/10.1172/jci.insight.158193.

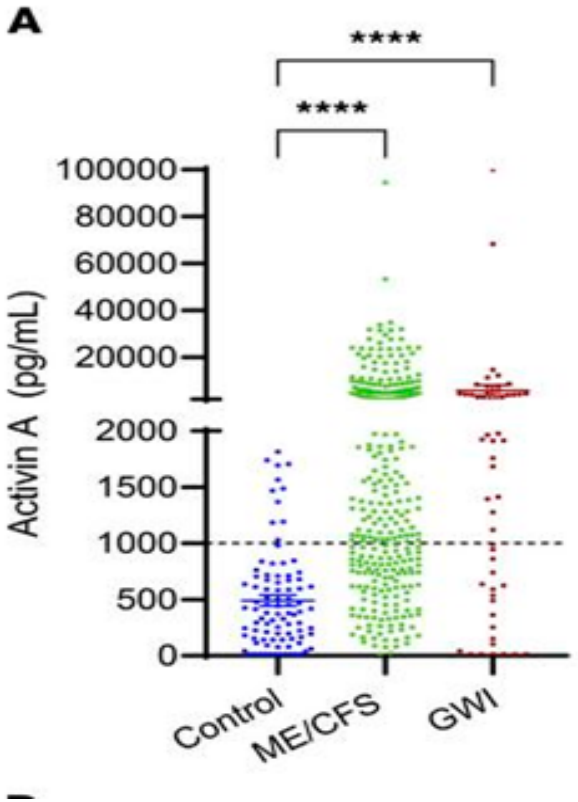
- ★ Intermediate between latent and lytic
- ★ EBV dUTPase: virus replication & ? immune dysfunction
- ★ EBV/ HHV-6 dUTPase Ab: 53% ME/CFS vs. 29% HC

Do dUTPases cause immune dysfunction?

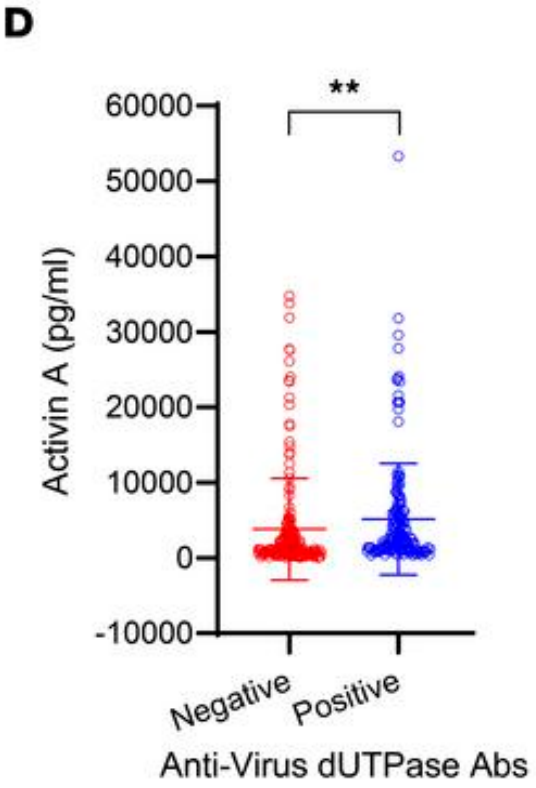
How do they cause immune dysfunction?

67% vs. 14%
above normal, p<0.001

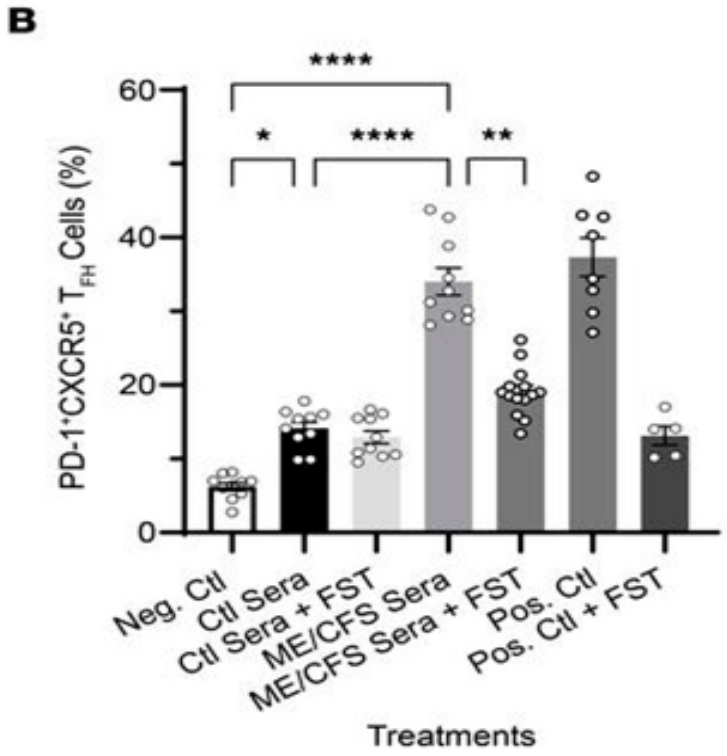
3809 pg/mL ± 500.8
vs. 5156 pg/mL ± 585.1,
p <0.01



Normal



Naive CD4 cells mature when exposed to ME/CFS sera



* dUTPase Ab+ ME/CFS sera has Activin A, dUTPase
* FST inhibits Activin A
* Activin A is sufficient to stimulate CD4 T-cell maturation
* Also, despite maturation, decreased function

Infection: what's possible?

* Re-define "active" EBV infection, leading to new tests
* Development of treatment targeting abortive lytic states

Immune exhaustion: CD8 T-cells

* If chronic viral infection = exhausted immune system?
* CD8 T-cells target viruses (& cancerous cells)
* Changes with exhaustion:

✓energy production/ use

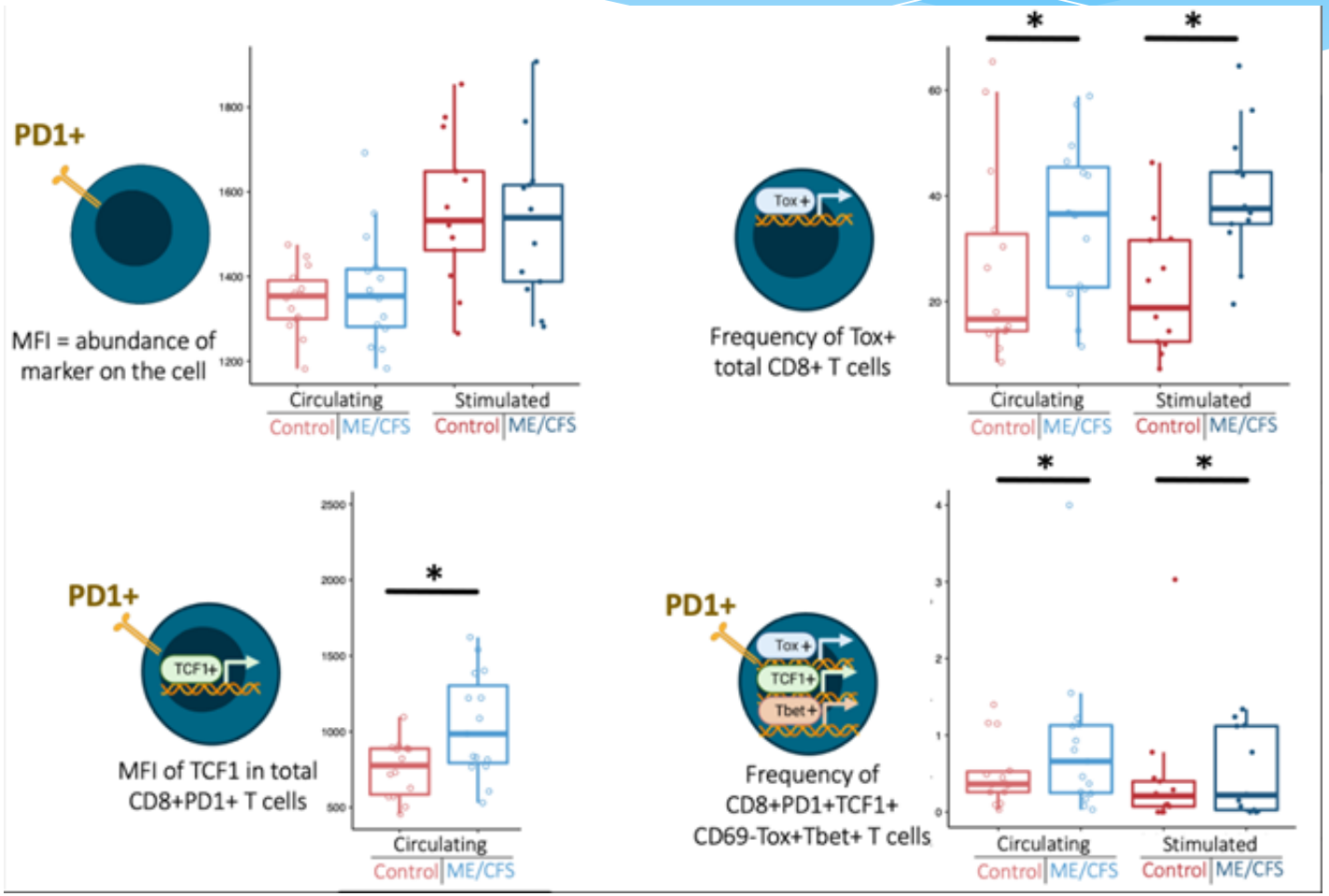
✓mitochondria electrical signals

Are there other changes that support exhaustion?

What can be done?

Immune exhaustion: cell markers

J. Maya, Cornell



Immune exhaustion: function decreased

L. Selin & A. Gil, Univ of Massachusetts

% of CD8 T-cells producing cytokines after stimulation ($p<0.01$)

	Healthy	Long COVID	ME/CFS
IFN-gamma	30%	6%	6%
TNF-alpha	33%	10%	8%
Inspiritol cases		N= 5	N=4
After Inspiritol + ? antiviral		Improved sx. Increased function	Improved sx. Increased function

Inspiritol: antioxidant/-inflammation/-bacterial/-viral

Inhaled (COPD, Asthma)

Minimal side effects (cough)

Immune exhaustion: what's possible?

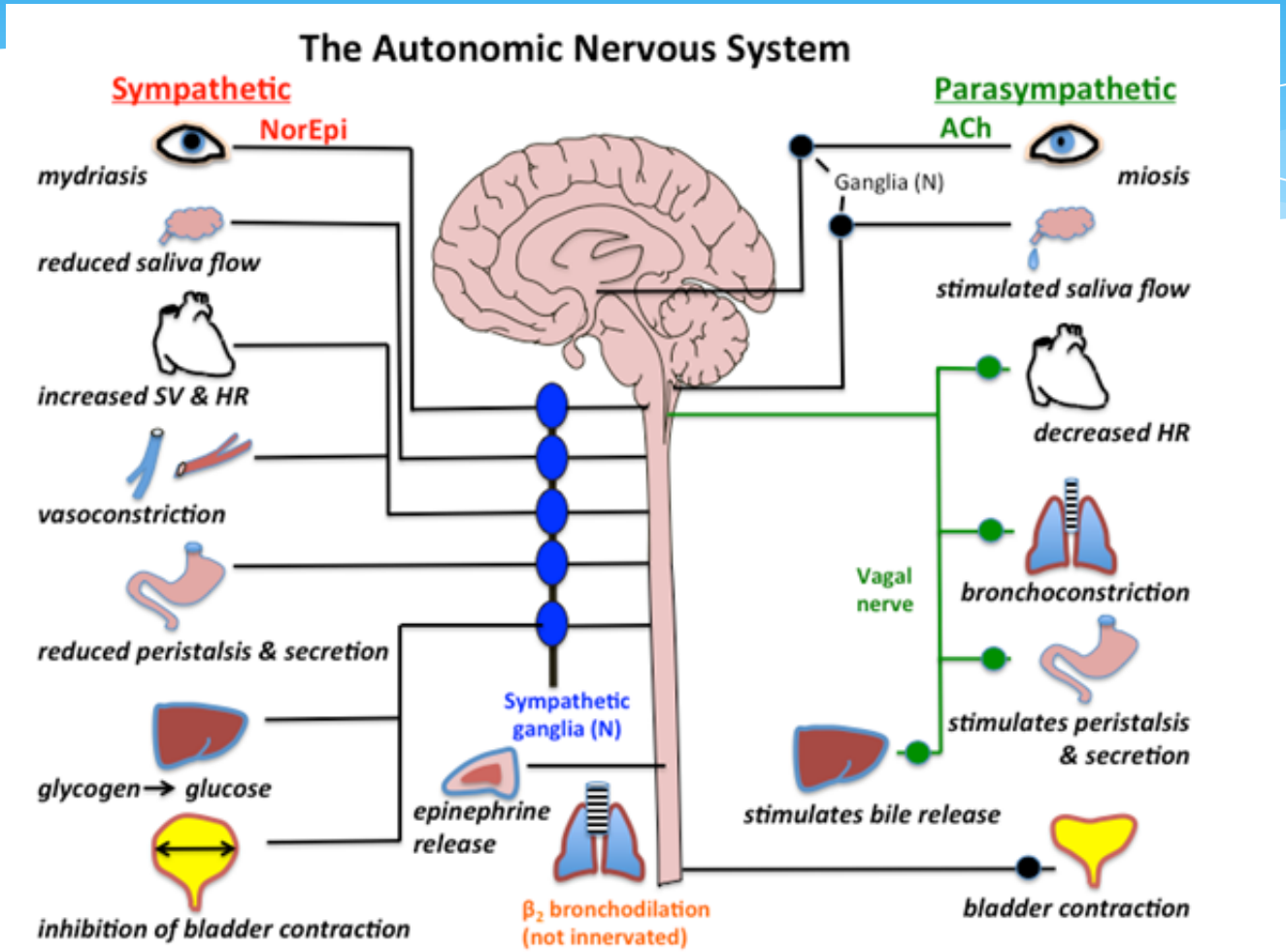
* Immune exhaustion as chicken instead of the egg

* Markers and/or function to help diagnose ME/CFS

* Improve T-cell exhaustion = may treat illness even if "chicken" unknown?
  a. Checkpoint inhibitors -block surface markers
  b. Gene editing: knock out/ silence genes associated with exhaustion

★ Synergy with antivirals? other meds?

Imbalance: what is the ANS?

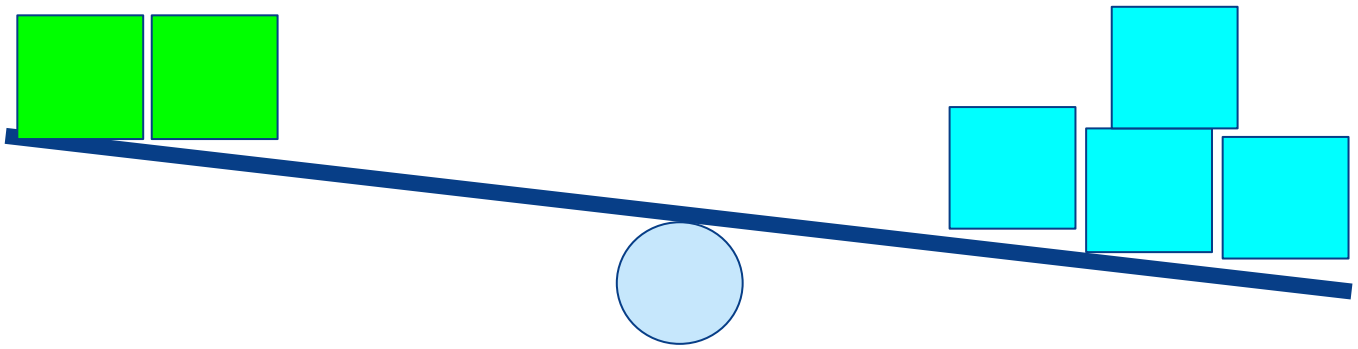


From: https://tmedweb.tulane.edu/pharmwiki/doku.php/introduction_to_the_ans

Imbalance: sympathetic predominance?

* Many ME/CFS symptoms suggest ANS dysfunction
* Objective finding examples:
  - Unrefreshing sleep linked to increased symp activity
  - Autoantibodies to adrenergic/ muscarinic receptors

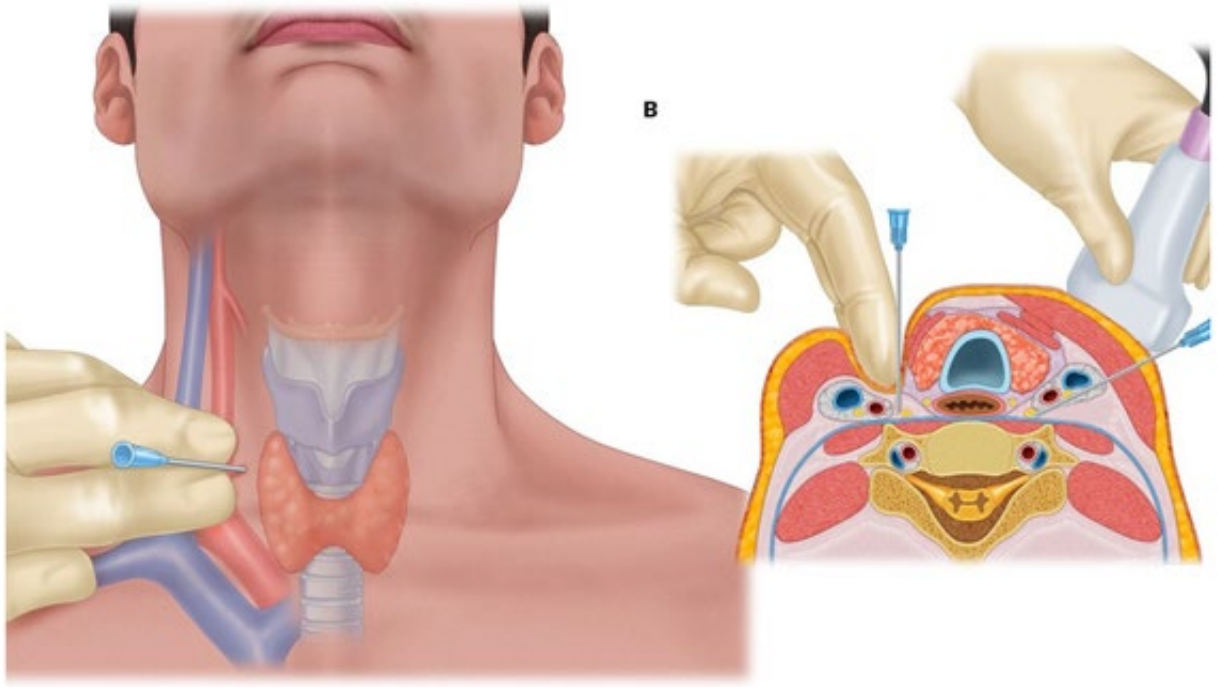
Parasympathetic **Sympathetic**



https://www.mayoclinic.org/tests-procedures/vagus-nerve-stimulation/about/pac-20384565

What is a stellate ganglion block (SGB)?

D. Duricka and L. Liu, Neuroversion



From: https://rapm.bmj.com/content/44/6/669

Standard procedure approved for pain syndromes, excess sweating, Raynauds

Block sympathetic signalling via stellate ganglia

SGB & ME/CFS: 2/ 5 cases

	Patient #1	**Patient # 2**
Age/ duration	62 / 18 yrs.	52/ 32 yrs.
Onset	Estradiol injection	Mono/ Hep A hospitalization
Symptoms	PEM/ cognitive issues	PEM/ body pain
Other diagnoses	Ind	Ind +Asthma, allergies, MCAS
Injection pattern	10 sets over 21 days	8 sets over 4 months
Improved symptoms	Multiple	Multiple + Co-morbid
Duration of improvement	At least 9 months	6 weeks
Outcome	95% pre-illness No further treatment	Relapsed with surgery; resumed treatment

Caution: not a trial, small sample size, SBG risks

What is transcutaneous auricular vagus nerve stimulation (taVNS)?

N. Clague-Baker, University of Liverpool, UK

Originally for treatment-resistant seizures/ depression

Stimulates parasympathetic signalling via vagus nerve

https://soterixmedical.com/research/tavns

taVNS and ME/CFS: feasiblity

- ★ 116 people, 75% Europeans, 50% sick 10+ year
- ★ Only 10% used 1+ year

- ★ 70% continued, 30% stopped
- ★ Main pros: 40% report improved PEM, cognition
- ★ Main cons: 15% headache, 10% skin irritation

Caution: costs, model, adjustment time, not = to implant

Imbalance: what's next?

* Encourage exploration of ANS role
* Need clinical trials for validation, refinement
* Use as diagnostic test to target treatment

Conclusion

* Studies replicating and/or reinforcing other studies

* Tests & treatments can be designed/ assessed now even if exact cause(s) and mechanism not yet known

To purchase video recordings & read summaries:
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