



International Society for CNS Clinical Trials and Methodology

Precision clinical trials: how to overcome the limits of DSM

Eric Lenze MD

Wallace & Lucille Renard Professor and Chair of Psychiatry

Washington University School of Medicine, St. Louis

Eric Lenze

Disclosure of Interest

Research Support (non-govt)

1. PCORI
2. COVID Early Treatment Fund
3. Emergent Ventures FastGrants

Speakers Bureau

n/a

Patents

Applied for patent for sigma-1 agonists in COVID-19 treatment

Consultant

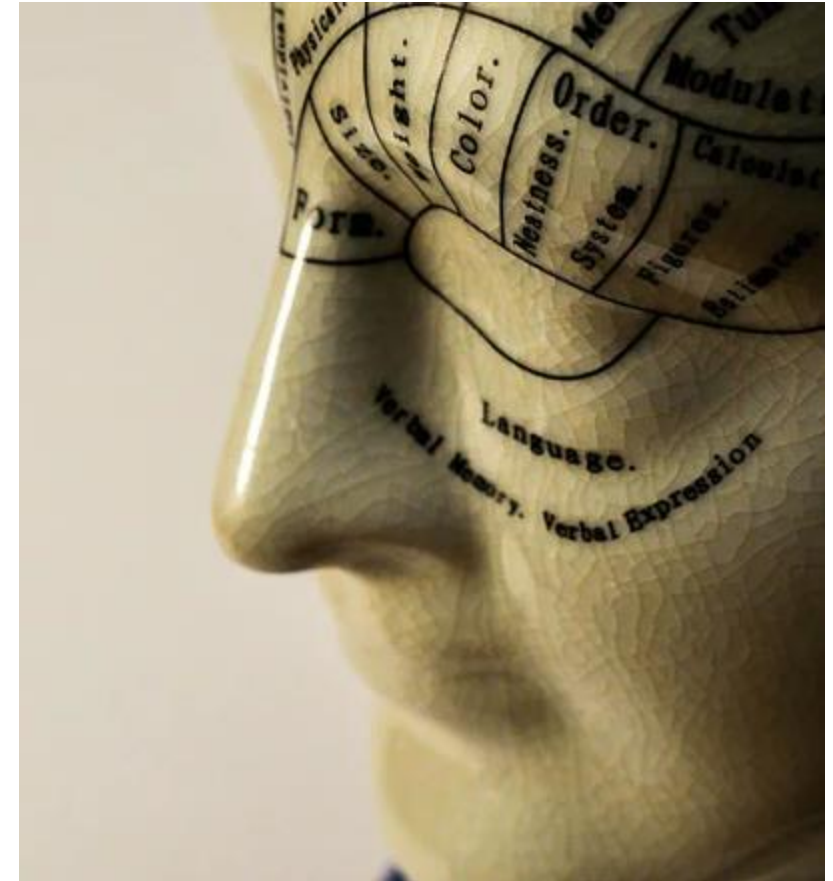
Prodeo, Boehringer-Ingelheim

I own no stocks or equity in any pharmaceutical company

Limits to the DSM approach to clinical trials

- Existing antidepressants are based on a DSM approach.
 - Inclusion: DSM criteria for MDD
 - Outcome: MADRS, HAM-D reify DSM criteria for MDD
- The DSM approach is a limitation for targeted agents.
- Why? Because DSM diagnosis \neq biological target.

[Mofsen et al, "When all else fails, listen to the patient" JMIR Mental Health 2019](#)



Example: senolytics for accelerated aging

nature medicine

Review Article | [Published: 11 August 2022](#)

Cellular senescence and senolytics: the path to the clinic

[Selim Chaib](#), [Tamar Tchkonja](#) & [James L. Kirkland](#) 

[Nature Medicine](#) **28**, 1556–1568 (2022) | [Cite this article](#)



Could Getting Rid of Old Cells Help People Live Disease-Free for Longer?

Researchers are investigating medicines that selectively kill decrepit cells to promote healthy aging

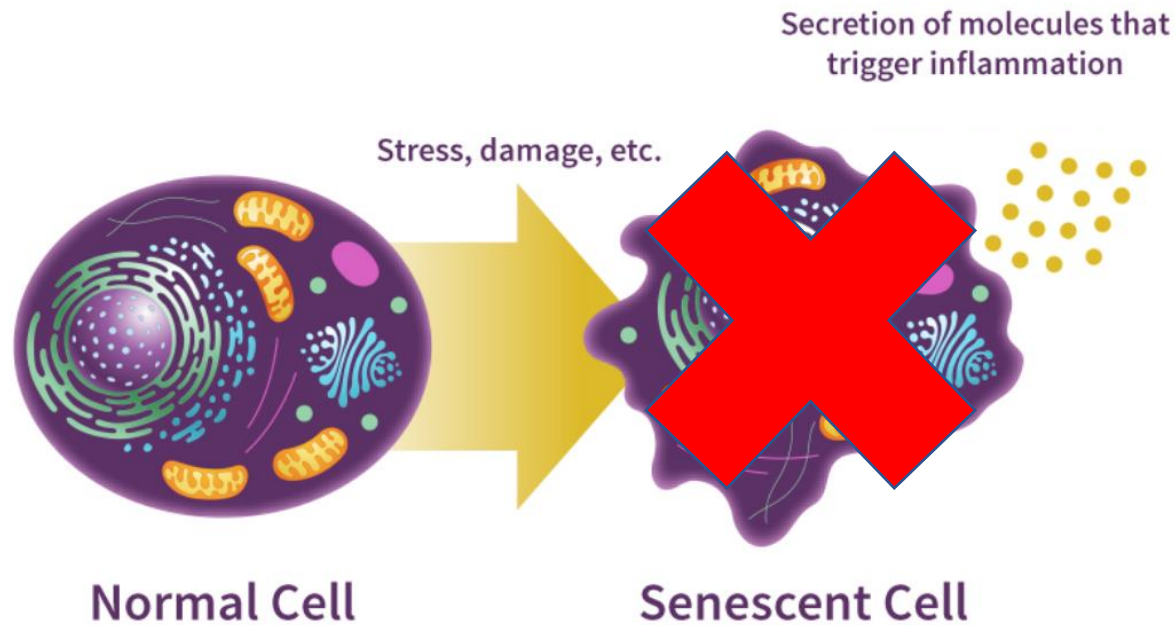
Amber Dance, Knowable Magazine

December 29, 2022



A growing movement is underway to halt chronic disease by protecting brains and bodies from the biological fallout of aging. Malte Mueller/Getty Images

Treatments affect a target: The example of senolytics

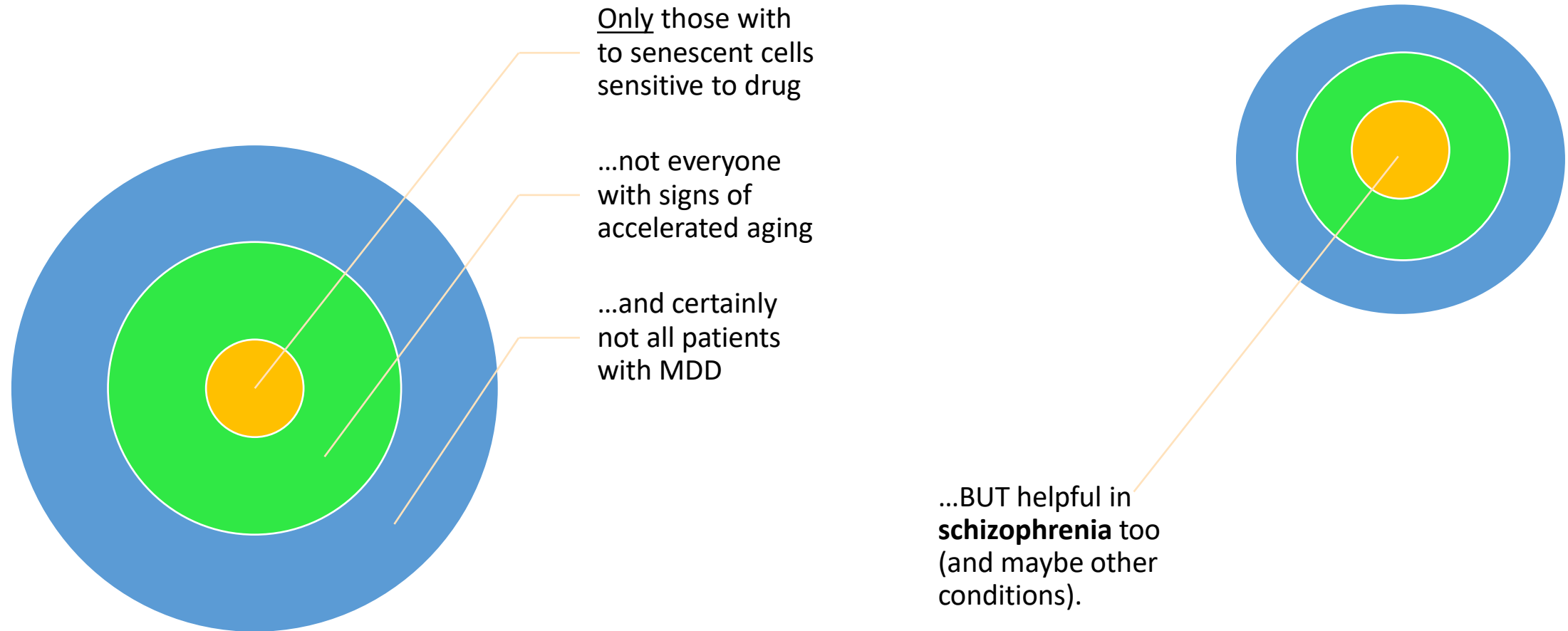


← Senolytics stop this.

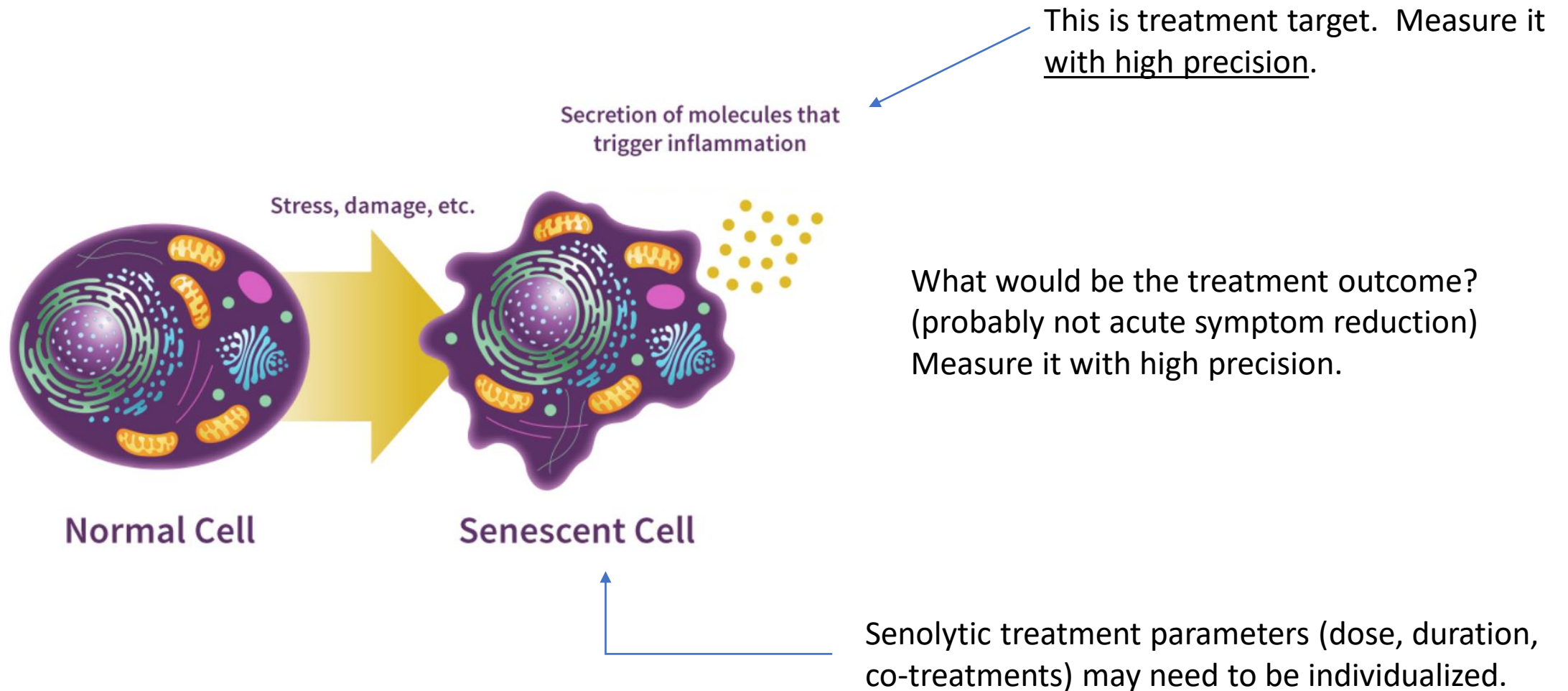
Senolytic drugs may be helpful in mental illnesses where accelerated aging leads to clinical, cognitive, and medical decline.

...if so, it would be via this target (stopping the secretion of inflammatory molecules).

Senolytics are expected to help patients based on pathophysiology, not DSM diagnosis



Challenges in trials of targeted treatments...



Clinical trial framework for targeted treatments

**Precision Clinical trial:
3 features**

**Treatment-
targeted
enrichment**

**Adaptive
treatment**

**Precise
measures**

Example in senolytic treatment

Patients who show treatment-induced changes in target (reduction in peripheral biomarker of senescence cell secretions) = population of interest.

Individually adjust the dose, duration, and cotreatments to maximize target engagement (and ensure tolerability) in that individual patient.

Measure both target (biomarker) and outcome (clinical effects of reversing accelerated aging) using measures with high test-retest reliability

[Lenze et al, "Precision clinical trials: a framework for getting to precision medicine for neurobehavioural disorders" J Psychiatry Neurosci 2021](#)

FDA guidance encourages precision medicine approaches in clinical trials.

