Precision clinical trials: how to overcome the limits of DSM

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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

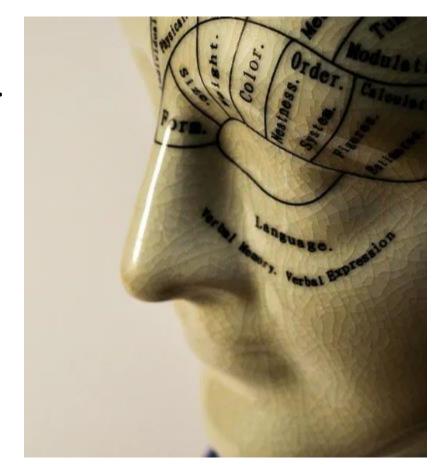
Consultant

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 <u>DSM approach</u>.
 - Inclusion: DSM criteria for MDD
 - Outcome: MADRS, HAMD reify DSM criteria for MDD
- The DSM approach is a limitation for targeted agents.
- Why? Because DSM diagnosis ≠ 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 Tchkonia & James L. Kirkland □

Nature Medicine 28, 1556–1568 (2022) Cite this article

Smithsonian

INNOVATION

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

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

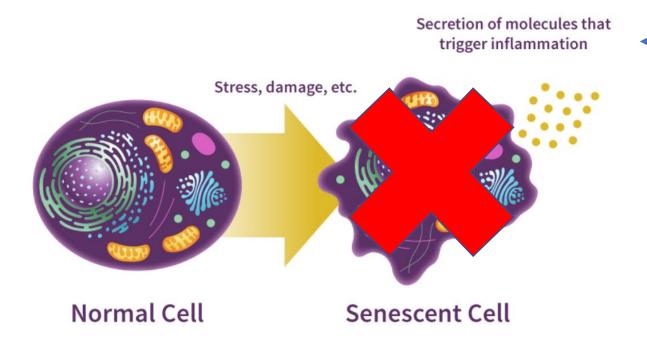
Amber Dance, Knowable Magazine

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 <u>target</u>: The example of senolytics



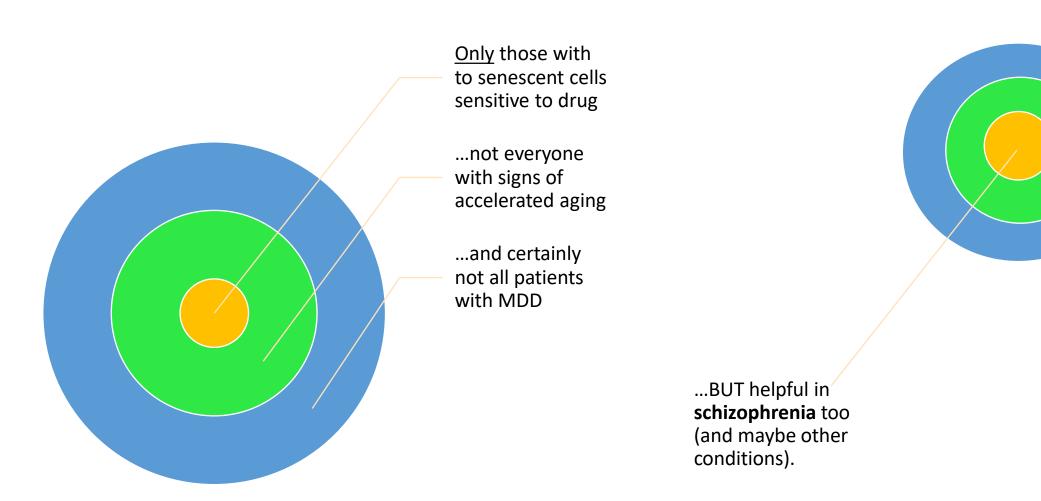
Senolytics stop this.

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

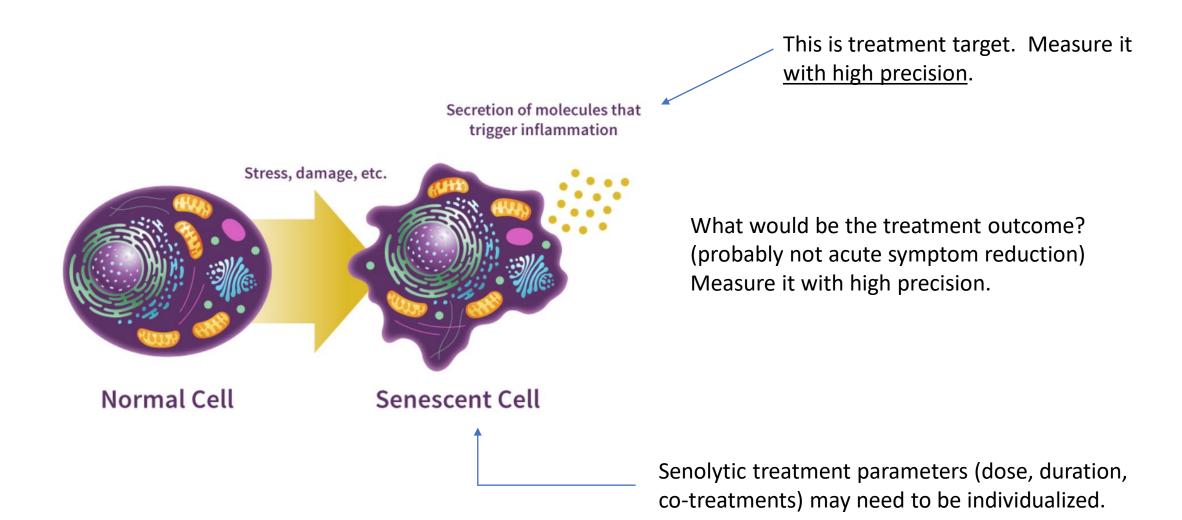
...if so, it would be via this target (stopping the secretion of inflammatory molecules).

Romashkan et al, National Institute on Aging Workshop: Repurposing drugs or dietary supplements for their senolytic or senomorphic effects: considerations for clinical trials. 2021

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

Treatmenttargeted 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.

Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products Guidance for Industry Methods for predictive enrichment

High-precision outcome assessments

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)

> March 2019 Clinical/Medical

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

> U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Center for Devices and Radiological Health (CDRH)

> > December 2009 Clinical/Medical