



Thoughts About Health Span

Andrew A. Nierenberg, MD

As we age, we tend to collect diseases and disorders. Some age better than others and those with serious mental illness tend to age and die 10 to 30 years earlier than the general population. Why and how does this happen? Why do our biological systems collapse? Are the diseases of aging inevitable? Can we hack the aging systems with realistic goals, not necessarily to live forever, but instead, to live longer with good health (ie, extend the health span)? Curious minds are working on it.¹

Major studies targeting aging are exploring whether the antidiabetic drug metformin can extend the health span (and maybe even lifespan) in people without diabetes, based on findings from

Andrew A. Nierenberg, MD, holds the Thomas P. Hackett, MD, Endowed Chair in Psychiatry at MGH, and is the Director of the Dauten Family Center for Bipolar Treatment Innovation, and the Director, Center for Clinical Research Education, MGH Research Institute, Massachusetts General Hospital; and a Professor of Psychiatry, Harvard Medical School.

Address correspondence to Andrew A. Nierenberg, MD, via email: psyann@Healio.com.

doi:10.3928/00485713-20190213-02

worms and mice.²⁻⁵ Justice et al.⁶ explore if the effects of metformin are due to changes in biomarkers (interleukin-6, tumor necrosis factor alpha-receptor I or II, C-reactive protein, *GDF15*, insulin, insulin-like growth factor 1, cystatin C, N-terminal pro b-type natriuretic peptide, and hemoglobin A1c).⁶ Lest you act prematurely and convince your doctor to prescribe metformin before the results are known, metformin can blunt exercise capacity.⁷

Another potential intervention proposed to extend the health span is nicotinamide riboside and pterostilbene.^{8,9} Although this combination targets energy metabolism and has been shown to extend the lifespan of worms and mice, no data have shown similar results in humans. One study has shown, however, that the combination increases nicotinamide adenine dinucleotide blood levels in humans.¹⁰ Despite the paucity of evidence, the combination is being sold as a supplement that targets longevity gene activation.

And what about our patients? Why do they die prematurely? One clue may be that, for example, patients with bipolar disorder have shorter telomeres than healthy controls.¹¹ Another clue may be the overlap between genes for psychiatric and cardiovascular risk.¹² Our patients also have challenges with regulating their diet, exercise, and sleep, resulting

in metabolic problems compounded by the medications that they are taking.

Advances in increasing the health span may change the way we and our patients live, but we still have a long way to go.

REFERENCES

1. Barzilai N, Cuervo AM, Austad S. Aging as a biological target for prevention and therapy. *JAMA*. 2018;320(13):1321-1322. doi:10.1001/jama.2018.9562.
2. De Haes W, Frooninckx L, Van Assche R, et al. Metformin promotes lifespan through mitohormesis via the peroxiredoxin PRDX-2. *Proc Natl Acad Sci U S A*. 2014;111(24):E2501-E2509. doi:10.1073/pnas.1321776111.
3. Martin-Montalvo A, Mercken EM, Mitchell SJ, et al. Metformin improves healthspan and lifespan in mice. *Nat Commun*. 2013;4:2192. doi:10.1038/ncomms3192.
4. Song J, Jiang G, Zhang J, et al. Metformin prolongs lifespan through remodeling the energy distribution strategy in silkworm, *Bombyx mori*. *Aging (Albany, NY)*. 2019;11(1):240-248. doi:10.18632/aging.101746.
5. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. *Cell Metab*. 2016;23(6):1060-1065. doi:10.1016/j.cmet.2016.05.011.
6. Justice JN, Ferrucci L, Newman AB, Aroda VR, Bahnon JL, Divers J, et al. A framework for selection of blood-based biomark-

- ers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. *Geroscience*. 2018;40(5-6):419-436. doi:10.1007/s11357-018-0042-y.
7. Paul AA, Dkhar SA, Kamalanathan S, Thabab MM, George M, Chandrasekaran I, et al. Effect of metformin on exercise capacity in metabolic syndrome. *Diabetes Metab Syndr*. 2017;11(suppl):S403-S406. doi:10.1016/j.dsx.2017.03.025.
 8. Imai S, Guarente L. NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol*. 2014;24(8):464-471. doi:10.1016/j.tcb.2014.04.002.
 9. Imai SI, Guarente L. It takes two to tango: NAD⁺ and sirtuins in aging/longevity control. *NPJ Aging Mech Dis*. 2016;2:16017. doi:10.1038/npjamd.2016.17.
 10. Dellinger RW, Santos SR, Morris M, Evans M, Alminana D, Guarente L, et al. Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD⁺ levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. *NPJ Aging Mech Dis*. 2017;3:17. doi:10.1038/s41514-017-0016-9.
 11. Powell TR, Dima D, Frangou S, Breen G. Telomere length and bipolar disorder. *Neuropsychopharmacology*. 2018;43(2):445-453. doi:10.1038/npp.2017.125.
 12. Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Transl Psychiatry*. 2017;7(1):e1007. doi:10.1038/tp.2016.261.