Book

Can we trust *The End of Alzheimer's*?

When faced with diseases that are currently incurable, like Alzheimer's disease, it is common for patients and family members to look for hope outside of the physician's office. A diagnosis can be frightening, and it is understandable that some people are motivated to pursue any intervention claiming a beneficial effect. As direct-to-consumer interventions for dementia have flourished, so has the need to critically evaluate the evidence supporting these options.

As a cognitive neurologist at a large memory centre, my colleagues and I are often approached about the book *The End of Alzheimer's* by Dale Bredesen. The book reviews his eponymous protocol, subtitled the *First Program to Prevent and Reverse Cognitive Decline*. The Bredesen protocol offers a plan combining several dietary supplements with detailed lifestyle changes and other targeted interventions (eg, against inflammation and toxins). The protocol has grown in popularity, even with high out-of-pocket cost to implement, and the book has appeared on many bestseller lists including those of *The New York Times*, *Wall Street Journal*, and Amazon.com. Physicians who recommend the Bredesen protocol often cite the three published studies by Bredesen, as well as his affiliations with respected academic medical centres. The Bredesen protocol makes strong claims of efficacy despite no other approaches being shown to definitively prevent or reverse cognitive decline; it is therefore necessary to carefully evaluate the existing clinical data to determine the strength of the evidence that guides the protocol.

In terms of study design, the three scientific papers first-authored by Bredesen (in 2014, 2016, and 2018) are all clinical case series that describe the outcome of participants who have adopted his intervention. Case series are inherently a descriptive type of research that offer limited evidence and are problematic when used to demonstrate the effectiveness of a medical therapy. Case series cannot accurately evaluate the effect of a new treatment because they are not designed to test hypotheses. Instead, clinical trials with control groups and randomisation are suited to determine the efficacy of a new therapeutic intervention. Despite the certainty inferred by the book's subtitle, there is no published study that tests or proves the hypothesis that the Bredesen protocol can prevent and reverse cognitive decline. His study design, combined with the particular intervention described, also presents the substantial potential for a placebo effect. Placebos can have greater effect sizes in patient improvement when the intervention is novel, complex, expensive, has high-status branding, and there is an expectation of benefit from either the participant or provider. Another consideration with the study design is that case series are highly vulnerable to selection bias from included or excluded participants.

In addition to study design, serious issues within the three articles constrain the quality of the science (table). Specifically, none of these articles includes a methods section, so readers are not informed of relevant aspects of the protocol (eg, which protocol elements were followed, what was the dose and duration) and these studies cannot be replicated. Further, the papers do not convey participant inclusion and exclusion criteria, which would provide greater context for possible selection bias and its extent. Notably, in the 2018 paper of 100 participants who received the interventions described by the Bredesen protocol, all reportedly improved. No data are provided on any non-responders nor information on the use of diagnostic criteria. Collectively, these caveats limit our understanding of the generalisability of the results. Readers are informed that participants with subjective cognitive impairment or mild cognitive impairment are included in the studies; however, both conditions can have causes unrelated to neurodegenerative processes. These studies are therefore not targeting a common underlying neuropathological process of Alzheimer's disease, as the papers suggest. Other essential elements of a clinical study do not appear in the publications, such as an explanation as to how testing measures were conducted and evaluated. For the cognitive evaluations, this omission raises questions of whether stated improvements

The End of Alzheimer's
Dale Bredesen
Avery, 2017
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For more on the **risks of ignoring scientific evidence** see **Editorial** *Lancet Neurol* 2019; **18:** 415

For **Dale Bredesen's first scientific paper** see *Aging* 2014; **6:** 707–17

For **Bredesen's second scientific paper** see *Aging* 2016; **8:** 1250–08

For **Bredesen's third scientific paper** see *J Alzheimers Dis Parkinsonism* 2018; **8:** 450

For more on **placebo responses** see *Osteoarthritis Cartilage* 2009; **17:** 1255–62

Caveats and limitations	Implications
Case series, descriptive study design	Observational data are not designed to test hypotheses and provide limited evidence of efficacy (level 4, grade C). Highly subject to selection bias and placebo effects
Reports do not include a methods section	Insufficient descriptions of participants and protocol variables (eg, intervention, dose, or duration), precluding study replication
Studies include participants with broad potential causes of cognitive issues	Protocol theoretically targets Alzheimer's disease. However, studies cannot assess impact on a common neuropathological process
Limited information on how cognitive testing measures were performed and evaluated	Raises questions on whether the stated participant improvements on cognitive measures reflect true changes, changes due to chance, or improved performance due to a practice effect
2018 paper includes a testing measure not validated in the literature	Uncertainty on whether the tool can measure the desired variables
Restricted or no discussion of study limitations in the reports	Do not present a balanced evaluation of proposed scientific findings to readers, potentially introducing partiality
Undisclosed financial conflicts of interest in the 2018 report	Potential for authors to have self-motivated interests for stated study findings not made apparent to readers; limits ability of readers to evaluate the presented data in a broader context
Articles appear either in predatory open access journals or publishers identified as predatory	Predatory journals can publish low-quality scientific reports that might mislead readers about the rigor of the study

Table: **Summary of concerns in three scientific articles evaluating the Bredesen protocol**

For more on **Beall's list** see https://beallslist.net and https://www.nature.com/news/controversial-website-that-lists-predatory-publishers-shuts-down-1.21328

For more on **predatory publishers** see https://digitalcommons.cedarville.edu/publishing/

For more on the **price of predatory publishing** see https://www.nytimes.com/2019/04/03/science/predatory-journals-ftc-omics.html

For the **WHO guidelines on risk reduction of cognitive decline** see https://www.who.int/mental_health/neurology/dementia/guidelines_risk_reduction/en/

For more on **brain health supplements** see https://www.aarp.org/content/dam/aarp/health/brain_health/2019/06/gcbh-supplements-report-english.doi.10.26419-2Fpia.00094.001.pdf

For more on **communicating with patients in the context of pseudomedicine for dementia and brain health** see *JAMA* 2019; **321:** 543–44

in neuropsychological testing scores reflect true changes due to the intervention, are due to chance variations in performance, or if they result from a practice effect from repeat testing. Indeed, many people with subjective cognitive complaints would be expected to show practice effects on cognitive testing. In the 2018 paper, the so-called Mental Symptoms Questionnaire is used, apparently a 284-point cognitive evaluation of some kind, although the tool is not cited or indexed in PubMed, which calls into question the validity of the tool to measure the desired variables.

Seven of the 11 references in the 2018 paper are from Bredesen's own work. The three articles do not contain a thorough discussion of study limitations. Only two of the three papers acknowledge the preliminary nature of these findings and call for controlled studies of the protocol. On clinicaltrials.gov, one actively recruiting study of the Bredesen protocol is reported (Reversal of Cognitive Decline, NCT03883633) and is listed as a case-only observational study without a control group, randomisation, or a study mechanism to account for a placebo effect.

Readers might not be aware that the three case series evaluating the Bredesen protocol appear in journals considered by some to be predatory open access journals. Predatory open access journals are scientific-sounding publications that hijack the open access model for profit. Common features are often high fees for authors to publish and low to non-existent editorial oversight of article content and quality. The journal *Aging*, where the first two articles were published, appears on the Beall's list of potential, possible, or probable predatory open access journals, compiled by academic librarian Jeffrey Beall. OMICS International, publisher of *The Journal of Alzheimer's Disease & Parkinsonism,* where the third article is found, has been identified as a predatory publisher. OMICS International was subject to a recent USD $50 million fine by the United States Federal Trade Commission for deceptive business practises, including "misleading authors about the legitimacy of its journals".

With these considerations, it is notable that the Bredesen protocol has been made commercially available; however, the authors do not disclose any conflicts of interest in their scientific reports. The 2018 paper does not include a conflicts of interest statement, though the report appeared after the publication of the book in 2017. In addition to potential gains from book sales, Bredesen is listed as Chief Science Officer for Apollo Health, a company offering Bredesen protocol assessments, laboratory tests, and access to trained practitioners for USD $1399 (packaged as ReCODE), and a monthly subscription plan including cognitive games and online support for additional fees. Additionally, Apollo Health intends to offer courses for physicians to become certified protocol providers. The Apollo Health website also links to LifeSeasons.com/recode, where tailored dietary supplements developed "in partnership with Dale Bredesen" for the protocol are sold for over USD $150 per month. As of the time of this writing, the company website includes the claims "First Real Hope for Alzheimer's" and "Hope through Science."

There are elements of the Bredesen protocol that could be beneficial and are largely free to patients. It is standard of care in dementia clinics to educate patients, without cost, on the lifestyle interventions for brain health that are supported to some extent in the scientific literature, including aerobic exercise, a Mediterranean diet, social and cognitive engagement, and management of cerebrovascular risk factors. Health insurance generally covers testing for reversible causes of cognitive change, such as thyroid disorders, vitamin B12 deficiency, or sleep apnoea. Some elements of the Bredesen protocol that have not been shown to be effective for brain health are the intensive, costly regimens of dietary supplements. A recent international consensus document concluded that "supplements have not been demonstrated to delay the onset of dementia, nor can they prevent, treat, or reverse Alzheimer's disease or other neurological diseases that cause dementia".

When presented with this information, there are people who continue to hold a strong belief in the protocol's efficacy. Belief formation is indeed a complex process that has been explored by psychologists and philosophers of science. Not all beliefs we hold are subject to rigorous skepticism, and not all beliefs are shaped by factual information. Skepticism is a central feature of scientific integrity and is essential when evaluating potential medical interventions. Elsewhere, I have suggested ways to address patient questions regarding such interventions and how to communicate with patients when their beliefs may not be formed by factual information or responsive to new data. Physicians often falsely assume that our patients only need to be educated on a topic to change their beliefs and actions; it is instead our responsibility to meet patients where they are in their beliefs and perceptions.

When carefully examined, multiple red flags appear in the scientific studies supporting the Bredesen protocol. To date, the evidence does not support its claim to prevent and reverse cognitive decline. Hope is important in the face of incurable diseases and intuitive interventions can be compelling. However, unsupported interventions are not medically, ethically, or financially benign, particularly when other parties might stand to gain.

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