



## LETTERS

Global fishing subsidies can contribute to overfishing.

Edited by Jennifer Sills

## WTO must ban harmful fisheries subsidies

Sustainably managed wild fisheries support food and nutritional security, livelihoods, and cultures (1). Harmful fisheries subsidies—government payments that incentivize overcapacity and lead to overfishing—undermine these benefits yet are increasing globally (2). World Trade Organization (WTO) members have a unique opportunity at their ministerial meeting in November to reach an agreement that eliminates harmful subsidies (3). We—a group of scientists spanning 46 countries and 6 continents—urge the WTO to make this commitment.

To curb overfishing, biodiversity degradation and loss, and CO<sub>2</sub> emissions, and to safeguard food and livelihoods, WTO members must prohibit fisheries subsidies that cause harm, such as those that lower the cost of fuel and vessel construction and those that provide price support to keep market prices artificially high (2). Subsidies to distant-water fishing fleets must be eliminated to prevent overfishing on the high seas and in waters under national jurisdiction. Such subsidies threaten low-income countries that rely on fish for food sovereignty (4, 5). Exceptions to the rules—known as special and differential treatment—should be considered for small-scale fishers that use

low-impact gears or that fish for subsistence, but only if decoupled from incentivizing overfishing (6).

An effective agreement must eliminate subsidies for fuel (7), distant-water and destructive fishing fleets (4, 5), and illegal and unregulated vessels in line with the aims of Sustainable Development Goal 14.6 (8). To ensure accountability, it should also support low-income countries' efforts to meet their commitments and transition to sustainable management. Finally, the agreement should require transparent data documentation and enforcement measures (9).

We call on the heads of state of the High Level Panel for a Sustainable Ocean Economy, the Comprehensive and Progressive Agreement for Trans-Pacific Partnership, and the United States–Mexico–Canada Agreement—who have already committed to eliminating harmful subsidies (10–12)—as well as other trade blocs and individual countries, to declare their support now for an agreement that enshrines these recommendations. WTO members must harness their political mandate to protect the health of the ocean and the well-being of society.

U. Rashid. Sumaila<sup>1,2</sup>, Daniel Skerritt<sup>1</sup>, Anna Schuhbauer<sup>1</sup>, Sebastian Villasante<sup>3</sup>, Andres M. Cisneros-Montemayor<sup>4</sup>, Hussain Sinan<sup>5</sup>, Duncan Burnside<sup>2</sup>, and 289 additional authors†

<sup>1</sup>Institute for the Oceans and Fisheries, University of British Columbia, Vancouver, BC, V6T 1Z4, Canada. <sup>2</sup>School of Public Policy and Global Affairs, University of British Columbia, Vancouver, BC, V6T 1Z4, Canada. <sup>3</sup>Cross-Research in Environmental

Technologies, Department of Applied Economics, University of Santiago de Compostela, Santiago de Compostela, 15782, Spain. <sup>4</sup>School of Resource and Environmental Management, Simon Fraser University, Burnaby, BC, V5A 1S6, Canada. <sup>5</sup>Marine Affairs Program, Dalhousie University, Halifax, NS, B3H 4R2, Canada. \*Corresponding author. Email: r.sumaila@oceans.ubc.ca †Full list of authors and affiliations can be found at [www.science.org/doi/10.1126/science.abm1680](http://www.science.org/doi/10.1126/science.abm1680).

## REFERENCES AND NOTES

1. D. Pauly *et al.*, *Nature* **418**, 689 (2002).
2. U. R. Sumaila *et al.*, *Mar. Pol.* **109**, 103695 (2019).
3. WTO, Negotiations on fisheries subsidies (2021); [www.wto.org/english/tratop\\_e/rulesneg\\_e/fish\\_e/fish\\_e.htm](http://www.wto.org/english/tratop_e/rulesneg_e/fish_e/fish_e.htm).
4. D. Tickler *et al.*, *Sci. Adv.* **4**, eaar3279 (2018).
5. E. Sala *et al.*, *Sci. Adv.* **4**, eaat2504 (2018).
6. A. M. Cisneros-Montemayor *et al.*, *Mar. Pol.* **69**, 229 (2016).
7. U. R. Sumaila *et al.*, *ICES J. Mar. Sci.* **65**, 832 (2008).
8. United Nations General Assembly, "Transforming our World: The 2030 Agenda for Sustainable Development" (2015).
9. M. D. Smith, *Science* **364**, 34 (2019).
10. High Level Panel for a Sustainable Ocean Economy, "Transformations for a sustainable ocean economy: A vision for production, protection and prosperity" (2020); [www.oceanpanel.org/ocean-action/files/transformations-sustainable-ocean-economy-eng.pdf](http://www.oceanpanel.org/ocean-action/files/transformations-sustainable-ocean-economy-eng.pdf).
11. M. A. Khan *et al.*, *J. Econ. Struct.* **7**, 1 (2018).
12. A. M. Villarreal, I. F. Fergusson, "NAFTA and the United States–Mexico–Canada Agreement (USMCA)" (Congressional Research Service Report, 2020).

## COMPETING INTERESTS

U.R.S. is an unpaid member of the Board of Directors of Oceana and Science Advisory Board Member of the Pew Charitable Trusts' Global Ocean Legacy Programme and has received funding from the High Level Panel for a Sustainable Ocean Economy and Oceana. S.V. has received funding from the "EQUALSEA—Transformative adaptation towards Ocean Equity" Project, under the European Horizon 2020 Program.

10.1126/science.abm1680

## Alzheimer's drugs: Does reducing amyloid work?

In his Perspective "Treatments for Alzheimer's disease emerge" (6 August, p. 624), D. J. Selkoe asserts that some trials testing potential treatments for Alzheimer's disease have shown "evidence of disease modification." He cites reductions in amyloid plaques (hypothesized to cause cognitive decline) and some modest reductions in cognitive decline shown in four potential drugs that target amyloid. However, hardly any trials have shown an effect, and even the trials with statistically significant results show effects that are too small to be clinically significant or to justify moving forward with the treatments.  $\beta$ -amyloid antibodies can lower amyloid plaques (extracellular aggregated insoluble  $\beta$ -amyloid), but available data show that decreasing amyloid plaques does not in itself lead to reduction in cognitive decline.

The data from six phase 2 or 3 trials of the four medications cited by Selkoe are available in peer-reviewed articles. Four trials were stopped for futility and one trial, lecanemab, was negative (1). Only one trial hit its primary endpoint (for donanemab) (2). The negative lecanemab trial did not meet its primary endpoint at 12 months, despite the potential advantage of a protocol change that created an imbalance in *APOE4* carriers, who experience faster cognitive decline. With only 30% of the treatment cohort composed of *APOE4* carriers compared with 71% of the placebo group, the placebo group would be expected to decline more quickly (3, 4). Selkoe claims that one gantenerumab phase 2 trial reduced amyloid and cognitive decline, but both reported phase 3 gantenerumab trials were stopped for futility and had no significant effects on primary or secondary outcomes (5) at 2 years. Selkoe characterizes a small trial of donanemab as “markedly” decreasing amyloid and “significantly” slowing cognitive decline. However, this trial showed only a 3.2-point benefit on a 144-point scale—half the trial team’s designated minimally clinically significant effect size (2)—and no significant effects on secondary cognitive and functional outcomes (6). One aducanumab trial, EMERGE (NCT02484547), showed a 0.39-point (23%) better outcome for the treatment group on the primary Clinical Dementia Rating (CDR-SB) scale outcome at 18 months, but the identical ENGAGE trial showed a 0.03-point (2%) worsening with treatment (7).

Selkoe speculates several reasons for failures of past trials but ignores what might be the most obvious: The treatment target ( $\beta$ -amyloid) itself may be wrong. Just as removing smoke does not extinguish a fire, reducing amyloid plaques may not affect the course of Alzheimer’s disease. Certainly, trial data do not support any clinical benefit of amyloid plaque reduction (8). Neither donanemab nor aducanumab trialists reported an association between amyloid reduction and individual participant clinical outcomes (2, 7). No comparable published results are available for lecanemab or gantenerumab. Furthermore, the amyloid cascade hypothesis proposes  $\beta$ -amyloid aggregation as an early disease trigger, preceding tau phosphorylation and accumulation (9). However, despite reducing amyloid plaques, donanemab failed to lower tau and also increased brain atrophy (10).

Alzheimer’s disease antibody trials represent the definitive test of the amyloid hypothesis of Alzheimer’s disease.

Objective appraisal of the clinical outcomes data suggests more a failure of hypothesis confirmation than successful translation of this disease model.

**Madhav Thambisetty<sup>1</sup>, Robert Howard<sup>2</sup>, M. Maria Glymour<sup>3</sup>, Lon S. Schneider<sup>4</sup>**

<sup>1</sup>Clinical and Translational Neuroscience Section, Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD 21224, USA.

<sup>2</sup>Division of Psychiatry, University College London, London W1T 7NF, UK. <sup>3</sup>Department of Epidemiology and Biostatistics, University of California, San Francisco, CA 94158, USA.

<sup>4</sup>Department of Psychiatry and the Behavioral Sciences, Department of Neurology, and the USC Alzheimer Disease Research Center, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA.

\*Corresponding author. Email: thambisetty@ mail.nih.gov

#### REFERENCES AND NOTES

1. C. J. Swanson *et al.*, *Alzheimers Res. Ther.* **13**, 80 (2021).
2. M. A. Mintun *et al.*, *N. Engl. J. Med.* **384**, 1691 (2021).
3. K. R. Murphy *et al.*, *Neuroimage* **78**, 474 (2013).
4. J. Qian, R. A. Betensky, B. T. Hyman, A. Serrano-Pozo, *Neurology* **96**, e2414 (2021).
5. S. Ostrowitzki *et al.*, *Alzheimers Res. Ther.* **9**, 95 (2017).
6. A. I. Levey, *N. Engl. J. Med.* **384**, 1762 (2021).
7. U.S. Food and Drug Administration, “Drug Approval Package: Aduhelm (aducanumab-awwa). Statistical Review and Evaluation NDA/BLA #: 761178” (2021); [www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/761178Orig1s000StatR\\_Redacted.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000StatR_Redacted.pdf).
8. S. F. Ackley *et al.*, *BMJ* **372**, n156 (2021).
9. E. S. Musiek, D. M. Holtzman, *Nat. Neurosci.* **18**, 800 (2015).
10. S. Ayton, *Eur. J. Neurol.* **28**, e67 (2021).

#### COMPETING INTERESTS

L.S.S. has received consulting or advisory fees within the past 3 years from Cortexyme, Cognition Inc, Eisai, Eli Lilly, IBC Ltd, Merck, Neurim Ltd, Roche/Genentech, Samus, Takeda, UCB; and has received grants or contracts from Biogen, Eisai, Eli Lilly, and Novartis related to the subject matter of this correspondence.

10.1126/science.abl8366

## Response

Thambisetty *et al.*’s assertion that “trial data do not support any clinical benefit of amyloid plaque reduction” in Alzheimer’s disease is not supported by close analysis of all publicly available trial data. Some amyloid- $\beta$  (A $\beta$ ) antibodies but not others have decreased amyloid deposits in brain regions serving cognition, accompanied by slowing of decline on some tests of cognition and activities of daily living. The US Food and Drug Administration’s (FDA’s) Clinical Pharmacology Review of aducanumab concluded that its reduction of amyloid plaques correlated with slowing of cognitive decline and that this “is consistent across all 6 other programs of A $\beta$  antibodies over the past decade” [(1), p. 30, see Fig. 5]. The FDA said the negative aducanumab ENGAGE trial (NCT02477800) was the only exception to this relationship, suggesting it was a “potential outlier or chance finding” [(1), p. 29].

The positive aducanumab EMERGE trial (NCT02484547) showed significantly less (–23%) cognitive decline on 10 mg/kg than placebo ( $P = 0.0120$ ) at 18 months. Statistically significant treatment effects were also observed for all three ranked secondary clinical endpoints and the tertiary endpoint. This was supported by statistically significant dose-dependent reductions of amyloid plaques and of cerebrospinal fluid phosphotau, a marker of tangles that correlate with cognitive decline [(2), pp. 1–2]. In post-hoc analyses of EMERGE, all chosen comparisons showed a positive effect of aducanumab over placebo (3).

In the negative (and non-identical) aducanumab ENGAGE trial (NCT02477800), the FDA noted that patients with the highest drug exposure had benefits on cognition and activities of daily living, like patients in the EMERGE trial with comparable drug exposure [(2), p. 3]. The FDA Clinical Pharmacology team did extensive trial simulations and concluded that the probability of the high dose group in EMERGE being a false positive was very low. They suggested that the negative high dose group in ENGAGE was likely a chance finding driven in part by the numerous patients who were enrolled before a late protocol amendment allowed *APOE4* carriers to receive the highest dose (10 mg/kg) of aducanumab. The FDA said the probability of observing the overall aducanumab findings under an assumption that the agent was equal to placebo “was extremely low” [(2), p. 5].

Thambisetty *et al.* point out that for donanemab and aducanumab, there was no association between amyloid lowering and individual patient clinical outcomes. But the FDA has stated that randomizing patients into specific dose groups is highly likely to achieve a balance across dose groups (i.e., at group-level) of known and unknown prognostic factors that could influence outcomes. If patients are randomized at group-level (as they were) but the relationships between endpoints are assessed at individual-level within a dose group, “such a balance (in prognostic factors) can no longer be guaranteed” [(1), p. 27]. So, variability among Alzheimer’s disease patients may be too great to expect consistent individual correlations with outcomes, but correlations were seen at group level.

The lecanemab Phase 2b trial used Bayesian design and narrowly missed its ambitious 12-month primary outcome, but at 18-months, it showed favorable drug-placebo differences of 27% less decline on one Alzheimer’s disease cognitive test and 56% less on another (4). However, during enrollment, the regulator prohibited *APOE4* carriers from receiving the highest dose. To

AD TK

adjust for this, the highest and next-highest dose groups were analyzed together, thereby achieving *APOE4* balance between treatment and placebo groups, and now the first cognitive measure showed 20% less decline on the drug (at a nearly significant  $P = 0.053$ ). Moreover, lecanemab reduced cognitive decline more in *APOE4* carriers than in patients without *APOE4* (4), suggesting potentially greater overall benefit if more *APOE4* carriers had been allowed to take the highest dose.

Donanemab in a phase 2 trial robustly lowered amyloid plaques and achieved its primary endpoint on a composite score of cognition and activities of daily living at 18 months ( $P = 0.04$ ), with nominal positive trends for two secondary cognitive outcomes. Prespecified analyses of Tau-positron emission tomography showed less tau accumulation in frontal and temporal cortices, an important marker of cognitive decline (5, 6).

Thambisetty *et al.* question the clinical meaningfulness of the findings across the trials of these antibodies, but the Alzheimer's disease field has no established quantitative guidelines for what constitutes clinical meaningfulness from a patient and family perspective. In one study of clinically meaningful change, a 1- to 2-point worsening in the Clinical Dementia Rating (CDR-SB) scale was the average change across cognitively normal to moderately severe dementia, but at the level of mild cognitive impairment,

a rise in CDR-SB of  $<1$  (.98) was deemed meaningful by judgment of clinicians (not of patients or caregivers) (7).

Based on 3 decades of Alzheimer's disease genetics, A $\beta$  accumulation is the fire, not the smoke. Clearing amyloid in other diseases (e.g., transthyretin) slows organ failure (8), and the above trial results suggest we are starting to see this happen in Alzheimer's disease. Thambisetty *et al.* suggest not moving forward with amyloid-targeted treatments despite growing evidence that these agents can benefit patients, even if only modestly as used so far.

**Dennis J. Selkoe**

Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital Harvard Medical School, Boston, MA 02115, USA. Email: dselkoe@bwh.harvard.edu

**REFERENCES AND NOTES**

1. FDA, "FDA clinical pharmacology review" (2021); [www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/761178Orig1s000ClinPharm\\_Redacted.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761178Orig1s000ClinPharm_Redacted.pdf).
2. FDA, "Office of Neurology's summary review memorandum" (2021); [www.accessdata.fda.gov/drugsatfda\\_docs/nda/2021/Aducanumab\\_BLA761178\\_Dunn\\_2021\\_06\\_07.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/Aducanumab_BLA761178_Dunn_2021_06_07.pdf).
3. Biogen, "Aducanumab ADPD 2021 efficacy presentation" (2021), p. 13; <https://investors.biogen.com/static-files/74641e1b-cd23-495e-8f29-f4ecac0a1126>.
4. C. J. Swanson *et al.*, *Alzheimers Res. Ther.* **13**, 80 (2021).
5. J. S. Sanchez *et al.*, *Sci. Transl. Med.* **13**, eabc0655 (2021).
6. M. A. Busche, B. T. Hyman, *Nat. Neurosci.* **23**, 1183 (2020).
7. J. S. Andrews *et al.*, *Alzheimers Dement.* **5**, 354 (2019).
8. D. Adams, M. Slama, *Curr. Opin. Neurol.* **33**, 553 (2020).

10.1126/science.abm3288

**NEXTGEN VOICES: SUBMIT NOW**

**Post-pandemic adjustments**

Add your voice to *Science*! In this NextGen Voices survey, a reader asks for your advice! Have you been in this situation or one like it? Do you have any tips that you would like to share? Become a NextGen Voices peer mentor by contributing your thoughts!

Dear NextGen Voices peer mentors,  
 I am so excited that my university is finally allowing us to come back to work in a semi-normal way this year. However, I know that some of my labmates have been exceptionally productive during our time working remotely, publishing papers and finding new grants. Meanwhile, I have been overwhelmed by the stress of being away from my family, who live in a poorer country that has been hit especially hard, while also trying to care for my young children. I haven't published anything, and applying for grants feels impossible. As we move forward, how can I get my already sparse early-career CV (and life!) back on track and compete with all the people who have been so productive during this difficult time?

Sincerely,  
 Playing Catchup

**To submit, go to [www.sciencemag.org/nextgen-voices](http://www.sciencemag.org/nextgen-voices)**

Deadline for submissions is 5 November. A selection of the best responses will be published in the 7 January issue of *Science*. Submissions should be 150 words or less. Anonymous submissions will not be considered.