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CHASING THE MAGIC BULLET FOR AD

Around 50 million people worldwide suffer from dementia. An estimated 5.7 million Americans have Alzheimer’s disease (AD) and the number is projected to reach 14 million by 2050 and 15 million by 2060. In the past 14 years, after the NMDA receptor inhibitor memantine (see Hans Jorg Moebius) approved by the Food and Drug Administration (FDA) to alleviate some symptoms in 2003, no new drugs have been approved for AD, i.e., there is no Disease Modifying Drug (DMD) approved for the treatment of AD so far.

It is clear that winning the battle against AD must involve a cocktail of drugs directed to several targets that cause AD, and changes in lifestyle habits such as diet, sleep habits and physical exercise, rather than a magic bullet, because it manifests itself in different ways among women, men, young, old, and people of different cultural, dietary, ethnic, genetic, life style, racial, social, and vocational backgrounds.

However, we seek to find the magic bullet undaunted by the commonsense and scientific rationale against such magic to capture the market of about $236 billion a year (cost of AD in US). The quest to effectively diagnose, treat and even prevent Alzheimer’s disease has become the intense focus of both scientists and philanthropists like Bill Gates (see Why diagnosing Alzheimer’s today is so difficult—and how we can do better).

According to a study presented by Biogen and Eisai at the Alzheimer’s Association International Conference in Chicago on 25 July 2018, an anti-amyloid antibody BAN2401 allegedly slowed the progression of the Alzheimer’s disease (AD) by reducing the amount of amyloid plaque accumulated in the brain in AD patients based on the failed hypothesis that targeting the symptom of accumulation of amyloid plaques in the AD brain could hold the
key to fighting AD. BAN2401 caused brain swelling among 10 percent of the patients. These results are similar to that of Aducanumab that seemed to work in a yearlong study showing a significant reduction in amyloid beta and slower cognitive decline in AD patients\(^7\).

Based on the current state of the research, introduction of a single disease-modifying agent for the treatment of AD will be a miracle.
GLOBAL EFFORT FOR HEALTH

About 4–7 million people per year die prematurely and hundreds of millions become ill from air pollution causing pain and suffering. It is estimated that about 1.5 °C rise in global temperature since preindustrial times. As dwindling fossil-fuel prices rise; economic, social, and political instability ensues unless a replacement energy infrastructure is developed well ahead of time. All of which can be eliminated by a 100% global conversion of the energy infrastructure to zero-emission energy system by 2050.

Different fuels emit different amounts of various pollutants and emissions locally causing health and environmental issues globally. Different countries contribute to the global pollution differently. Therefore, it is essential to think globally and act locally to curb the pollution caused by the rich and greedy in their native habitats affecting every life form globally.

Individual countries are developing clean energy policies, and more than half the world’s countries signed a United Nations treaty called the Paris Agreement in April 2016, agreeing to take action to limit the global pollution causing destabilization of the life and extinction of certain life forms on earth. Electricity production using energy from the sun, wind, or water for all industries, including transportation, is a key component of any clean-energy plan. The transformation of the all-purpose energy infrastructure (electricity, transportation, heating, cooling, industry, agriculture, forestry, fishing, etc.) powered by Business As Usual (BAU) power to the infrastructure powered by Wind, Water, and Sunlight (WWS) reduces all-purpose end-use load by 42.5% because the work: energy ratio of WWS electricity exceeds that of combustion (23.0%), WWS requires no mining, transporting, or processing of fuels (12.6%), and WWS end-use efficiency exceeds that of BAU (6.9%). Conversion to WWS powered infrastructure creates 24.3 million more jobs than the number of jobs lost; and avoids premature air-pollution deaths of about 4.6 million/year today and estimated deaths of about 3.5 million/year in 2050, about $22.8 trillion/year (12.7¢/kWh-BAU-all-energy) in 2050 air-pollution costs, and about $2.85 trillion/year (15.8¢/kWh-BAU-all-energy) in 2050 climate costs; stabilizes energy prices because the fuel costs are zero; reduces power disruption; increases access to energy; and avoids the estimated global pollution based temperature increase of about 1.5 °C.

Across the globe, cities are tackling climate change by shifting away from coal, oil, and natural gas. One hundred-sixty-two cities like Reykjavik and Zurich have already quit using fossil fuels to produce power, and others plan to cut back. In US, Aspen in Colorado, Greensburg in Kansas, Burlington in Vermont, Kodiak Island in Alaska, and Rock Port in Missouri have successfully made the switch to 100 percent renewables by boosting clean power sources and eliminating fossil fuels which produce pollution including CO2.


Human beta-secretase (BACE) and BACE inhibitors: progress report https://www.ncbi.nlm.nih.gov/pubmed/16712492

A number of agents are studied so far, e.g., γ-secretase inhibitors such as Semagacestat (LY450139), and β-secretase inhibitors such as CTS-21166 (CoMentis), PF-05297909 (Pfizer), LY2886721 ( Lilly), A2D3293 (AstraZeneca), MK-8931 (Merk), etc.; α-secretase stimulators, muncaricin receptor 1 (M1) agonists, and selective Aβ42-lowering agents (SALA); Aβ42 aggregation blockers, e.g., Trimiprossate, Cloiquinol, PBT2, Colostrinin, anti-Aβ42 antibodies such as Gantenerumab, Solanezumab, Bapinezumab, etc.; Tau phosphorylation and aggregation inhibitors such as GSK-3 inhibitors and antibodies; nerve growth factor (NGF) stimulators, e.g. luteolin, xalofen, gamma aminobutyric acid (GABA) receptor modulators, e.g. SGS-742, NRG-97-1, AC 3933; serotonin reuptake and somatostatin secretion stimulants, e.g. FK 960; astrocyte-modulating agents (ONO 2506), phosphodiesterase 4 inhibitors (MK 0952), and cannabinoid agonists (AVE-1652)

REFERENCES AND NOTES


4. Defining and labeling disease-modifying treatments for Alzheimer's disease, Alzheimer's & Dementia, Volume 5, Issue 5, Pages 406–418 (September 2009) "Disease modification can be defined as treatments or interventions that affect the underlying pathophysiology of the disease and have a beneficial outcome on the course of AD. In a clinical trial the criteria for affecting the underlying cause of the disease can be supported by demonstrating an effect on a biomarker such as medial temporal atrophy on magnetic resonance imaging (MRI) or diminished tau or phospho-tau levels in cerebrospinal fluid. The claim for a beneficial effect on the clinical course of AD is supported by a drug-placebo difference on the primary clinical outcomes of the clinical trial. A statistically significant correlation between the biomarker outcome and the clinical trial outcome would support the claim that these are based on the same underlying mechanism."


5. Several disease-modifying therapeutic strategies for AD have emerged so far. Just a few to name: Eisai and Biogen’s oral BACE inhibitor elenbecatstat was able to demonstrate a reduction in amyloid beta levels in AD patients- the first time a BACE inhibitor to show a significant effect on amyloid beta levels in patients, but it failed to slow the decline of clinical symptoms. Janssen terminated trials of atabacestat. Merck halted a phase 3 trial of verubecestat. Meanwhile, Agen and Banner Alzheimer’s Institute launched a global prevention program using the BACE inhibitor CENP20. Novartis, Agen and Banner aim for Alzheimer’s prevention with new BACE trials https://www.fiercebiotech.com/biotech/eisai-biogen-s-bace-drug-towers-amyloid-levels-but-not-alzheimer’s-symptoms;

Scientists found that reduced levels of a protein called Rheb result in spontaneous symptoms of memory loss linked to increased levels of BACE1 protein known to be elevated in the brains of Alzheimer’s disease patients. Forebrain Rheb depletion promotes aging-associated cognitive defects. Forebrain Depletion of Rheb Elicits Spatial Memory Deficits in Mice. Neurobiology of Aging, 2016; DOI: 10.1016/j.neurobiolaging.2016.11.006; https://www.sciencedaily.com/releases/2016/12/161207160040.htm


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Review of the advances in treatment for Alzheimer disease: strategies for combating BETA-amyloid protein, Neurobiology;33(1):47-58 (2018) "Progress in identifying the molecular basis of AD may provide better models for understanding the causes of this neurodegenerative disease." http://creativecommons.org/licenses/by-nc-nd/4.0/


Why Alzheimer’s Drugs Keep Failing - Scientific American

Subjective Cognitive Decline (SCD) in individuals with unimpaired performance on cognitive tests may represent the first symptomatic manifestation of Alzheimer’s disease (AD) (see Subjective Cognitive Decline (SCD) at https://www.linkedin.com/pulse/subjective-cognitive-decline-scd).

Alzheimer’s disease risk impacted by the liver, diet: Research shows the liver could contribute to Alzheimer’s risk by failing to supply key lipids to the brain https://www.sciencedaily.com/releases/2018/07/180724174225.htm

Plasmalogens are created in the liver and are dispersed through the blood stream in the form of lipoproteins, which also transport cholesterol and other lipids to and from cells and tissues throughout the body, including the brain. Reduced levels of plasmalogens are associated with an increased risk of Alzheimer’s Disease. ScienceDaily, 24 July 2018

Clinical Trial Breakthrough for New Alzheimer’s Drug | Fortune

New Alzheimer’s drug may slow decline, researchers report - NBC News

Trial of new Alzheimer's drug shows promise results THE WASHINGTON POST

New Alzheimer’s drug shows hints of promise in inventive trial - Science

Alzheimer’s: New hope for drug, but it’s still early - CNN

New Alzheimer’s Drug Shows Big Promise in Early Trial Results - The NY TIMES

100% Clean and Renewable Wind, Water, and Solar Energy Roadmaps for 139 Countries of the World


The term “think global, act local” was first used by the environmental movement in the 1960s and 70s. It referred to the need to be aware about worldwide environmental issues such as pollution, and then to take action to address these issues by making changes in local household and community, which even more relevant in the flattened, interconnected, 21st century global community where human rights; income inequality and poverty alleviation; gender equality; free and open Internet access; sustainable development; terrorism; freedom of movement and immigration; anti-globalization in the form of nationalism, isolationism and xenophobia; prevention and cessation of conflicts between countries; elimination of weapons of mass destruction; and other innumerable known, knowable, and unknown issues; along with the persistent diffuse global pollution caused locally by the rich industrialized countries followed by the poor countries aspiring to bring the life-style of the rich to the local poor.


A Global Transition to Clean Energy: Challenges and Opportunities
Comparing the amount of CO2 emitted per unit of energy output or heat content.

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<tr>
<th>Fuel Type</th>
<th>Pounds CO₂ Per Million Btu</th>
<th>Kilograms CO₂ Per Million Btu</th>
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<tbody>
<tr>
<td>Coal (anthracite)</td>
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<td>Coal (bituminous)</td>
<td>205.7</td>
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</tr>
<tr>
<td>Coal (lignite)</td>
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<tr>
<td>Coal (subbituminous)</td>
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<tr>
<td>Diesel fuel and heating oil</td>
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<tr>
<td>Gasoline (without ethanol)</td>
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<tr>
<td>Propane</td>
<td>139.0</td>
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</tr>
<tr>
<td>Natural gas</td>
<td>117.0</td>
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</tbody>
</table>

For homes and businesses

Are you wasteful or resourceful? [Link]

Other renewable energy options include wind, water, and sunlight.

100% Clean and Renewable Wind, Water, and Sunlight All-Sector Energy Roadmaps for 139 Countries of the World [Link]

Which Cities In the World Are Closest to Nixing Fossil Fuels? [Link]
O Sun, God, Sanatr!  
Thou dazzling fount of life—penetrating light!  
Sublime mystery spreading from afar!  
Sanatr became that burst too potent on the sight!  
This radiant type of strength and youth!  
Glowing eternally!

Go slow dhow!  
All luminaries get illuminated by His Illumination!  
The whole Universe is enlightened by His light!  
—Kathapanand

<table>
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<tr>
<th>Natural Gas</th>
<th>Industrial fuels and others not listed above</th>
<th>Nonfuel uses</th>
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<tr>
<td></td>
<td>Flared natural gas</td>
<td>Asphalt and Road Oil</td>
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<td>Petroleum coke</td>
<td>Lubricants</td>
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<td></td>
<td>Other petroleum &amp; miscellaneous</td>
<td>Petrochemical Feedstocks</td>
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<td></td>
<td>Nonfuel uses</td>
<td>Special Naphthas (solvents)</td>
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<td></td>
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<td>Waxes</td>
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<td>Bituminous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subbituminous</td>
</tr>
</tbody>
</table>

### Propane
- Price: $12.70/gallon
- Price: $5.76/gallon
- Price: $139.05
- Price: $63.07

### Butane
- Price: $14.80/gallon
- Price: $6.71/gallon
- Price: $143.20
- Price: $64.95

### Butane/Propane Mix
- Price: $13.70/gallon
- Price: $6.21/gallon
- Price: $141.12
- Price: $64.01

### Home Heating and Diesel Fuel (Distillate)
- Price: $22.40/gallon
- Price: $10.16/gallon
- Price: $161.30
- Price: $73.16

### Kerosene
- Price: $21.50/gallon
- Price: $9.75/gallon
- Price: $157.20
- Price: $71.30

### Coal (All types)
- Price: $4,631.50/short ton
- Price: $2,100.82/short ton
- Price: $210.20
- Price: $95.35

### Natural Gas
- Price: $117.10/thousand cubic feet
- Price: $53.12/thousand cubic feet
- Price: $117.00
- Price: $53.07

### Gasoline
- Price: $19.60/gallon
- Price: $8.89/gallon
- Price: $157.20
- Price: $71.30

### Other transportation fuels
- Price: $26.00/gallon
- Price: $11.79/gallon
- Price: $173.70
- Price: $78.79

### Flared natural gas
- Price: $120.70/thousand cubic feet
- Price: $54.75/thousand cubic feet
- Price: $120.60
- Price: $54.70

### Petroleum coke
- Price: $32.40/gallon
- Price: $14.70/gallon
- Price: $225.10
- Price: $102.10

### Other petroleum & miscellaneous
- Price: $22.09/gallon
- Price: $10.02/gallon
- Price: $160.10
- Price: $72.62

### Petroleum coke
- Price: $26.34/gallon
- Price: $11.95/gallon
- Price: $166.70
- Price: $75.61

### Lubricants
- Price: $23.62/gallon
- Price: $10.72/gallon
- Price: $163.60
- Price: $74.21

### Petrochemical Feedstocks
- Price: $24.74/gallon
- Price: $11.22/gallon
- Price: $156.60
- Price: $71.03

### Special Naphthas (solvents)
- Price: $20.05/gallon
- Price: $9.10/gallon
- Price: $160.10
- Price: $72.80

### Waxes
- Price: $21.11/gallon
- Price: $9.57/gallon
- Price: $160.10
- Price: $72.62

### Anthracite
- Price: $5,685.00/short ton
- Price: $2,578.68/short ton
- Price: $228.60
- Price: $103.70

### Bituminous
- Price: $4,931.30/short ton
- Price: $2,236.80/short ton
- Price: $205.70
- Price: $93.30

### Subbituminous
- Price: $3,715.90/short ton
- Price: $1,685.51/short ton
- Price: $214.30
- Price: $97.20
Lignite 2,791.60/short ton 1,266.25/short ton 215.40 97.70
Coke 6,239.68/short ton 2,830.27/short ton 251.60 114.12
Other fuels
Geothermal (average all generation) NA NA 16.99 7.71
Municipal Solid Waste 5,771.00/short ton 2,617.68/short ton 91.90 41.69
Tire-derived fuel 6,160.00/short ton 2,794.13/short ton 189.54 85.97
Waste oil 924.0/barrel 419.12/barrel 210.00 95.25

Source: U.S. Energy Information Administration estimates.
Note: To convert to carbon equivalents multiply by 12/44. Coefficients may vary slightly with estimation method and across time.

https://www.rt.com/search?q=climate+change&type