Why Isn't There a Cure or Treatment for Dementia?

PAC Research Corner
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A recent Washington Post article outlined some of the issues facing the field of dementia;[1] we will look at these through the Positive Approach® lens.

It's been a tough year in the world of experimental drug research on dementia. On January 8th, pharmaceutical giant Pfizer announced it was ending its research efforts to develop new drugs for both Alzheimers and Parkinsons diseases.[2] The next day, a study published in a leading medical journal, JAMA, reported yet another experimental drug failure.[3] In late September of 2017, Axovant Sciences, a clinical-stage biopharmaceutical company that focuses on neurologic conditions, announced the clinical trial of its investigational drug for patients with mild to moderate Alzheimer's disease (AD) had failed to show improvement for either motor function or cognition[4]. In truth, the FDA has approved no new disease-modifying medications for Alzheimers Disease, the most common form of dementia, since 2003. In fact, the overall success rate of the 413 trials during 2002 to 2012 showed a 99.6% failure to modify the disease.[5]

With no cure on the horizon, one of the more common questions we field at PAC is some form of this: Why hasn't science found a cure or at least a treatment for dementia? The short answer is that neuroscience and diseases of the brain are highly varied in type, complicated to examine, and expensive and challenging to find patients to study.

First, neuroscience and diseases of the brain are highly varied in type. Growing up in the 1970s, a similar question was posted of cancer research—why haven't we found a cure for cancer? Today, the general population may be more informed to understand that cancer is a collective term (a syndrome) for more than 100 types of cancer; each type has its own cause, and thus, its own treatment, prognosis, and survival rate. Those of you in our PAC Community know something similar about dementia that many do not understand: that dementia is the umbrella term, or a syndrome (a collection of symptoms), for the more than 120 different types, forms, or causes of dementia. Specifically, dementia is the term for a number of neurological conditions with the major symptom being global decline in brain function, ultimately leading to brain failure. For us to find the cure for different types of dementia, we will first need to better understand all the types, causes, and health trajectory of each.

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[1] Johnson, C. Y. (2018, Jan) Why coming up with a drug for Alzheimer's is so devilishly hard. *Washington Post,* Retrieved from https://www.washingtonpost.com/news/wonk/wp/2018/01/12/why-coming-up-with-a-drug-for-alzheimers-is-so-devilishly-hard/?utm_term=.aa3b91a6140a.
[2] https://www.npr.org/sections/thetwo-way/2018/01/08/576443442/pfizer-halts-research-efforts-into-alzheimers-and-parkinsons-treatments.
[3] Atri, A., Frölich, L., Ballard, C., et al (2018). Effect of idalopirdine as adjunct to cholinesterase inhibitors on change in cognition in patients with Alzheimer Disease: Three randomized clinical trials. *JAMA, 319* (2), 130-142. Retrieved March 8, 2018 from https://jamanetwork.com/journals/jama/article-abstract/2668349?redirect=true.
[4] http://investors.axovant.com/news-releases/news-release-details/axovant-announces-negative-results-intepirdine-phase-2b-headway.
[5] Cummings, J. L., Morstorf, T., and Zhong, K. (2014). Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimer's Disease Research and Therapy, 6* (4), 37.

Here's a positive perspective: although cancer was first recorded in 1500 BC[6], science took more than 2,000 years to identify the 100 types of cancer. By comparison, the first description of a person with dementia was by German physician Alois Alzheimer in 1906.[7] In just 112 years—not 2,000 years—science has identified the vast majority of the types, causes, and forms of dementia. In the world of medical research, dementia is a relative newcomer. Especially when considering that for many of those 112 years, *dementia* was either misdiagnosed or simply accepted as part of the aging process. In other words, dementia just hasn't been on the radar screen of most medical researchers.

The second reason why science has failed to produce substantive results in a cure for dementia is that all the dementias are a brain disease and, simply put, conducting neuroscience is difficult.[8] The brain is not an easy organ to access. A physician cannot simply take repeated tissue samples of the brain to see if the drug is working, nor can one repeatedly access the brain for examination. Further, to complete the picture for even a single area of the brain, large, interlinked datasets are required. Novel hardware and software must be invented to sufficiently simulate the brain.[9] Every year, neuroscientists are developing new ways of classifying and simulating brain disease, which will lead to better diagnosis and more effective drug discovery.

The third and fourth reasons why there is no cure are related. Clinical trials are long and expensive. To get patients before significant brain tissue loss occurs is the key. However, early diagnosis is hard. Teepa (and science!) tell us that *dementia = brain failure.*[10] Brain failure is more than just plaques and tangles; brain failure is progressive atrophy and tissue loss. Getting people diagnosed early is difficult enough; getting some of these into a clinical trial is harder.

Early diagnosis begins with both public awareness and practitioner awareness. One study estimated that as many as 50% of folks over the age of 50 may be living with an unrecognized dementia.[11] A recent study surveyed general practitioners' (GP) attitudes toward early diagnosis of dementia. Specifically, researchers looked at practitioners' confidence levels of early diagnosis, giving advice, perceived benefits of early diagnosis, and their training levels around dementia and overall knowledge. Researchers found that older practitioners had better information, but also tended to have a more skeptical view about the benefits of early diagnosis than did the younger practitioners.[12] Other studies found that GPs are reluctant to make a diagnosis of dementia and may unconsciously hesitate to do so.[13] Furthermore, a 2001 study found that in a survey of 1,005 GPs, almost

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[6] Sudhakar, A. (2009). History of cancer, ancient and modern treatment methods. *Journal of Cancer Science and Therapy, 1*, (2), 1–4. Retrieved March 8, 2018 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2927383/.
[7] Alzheimer, A. (1907). About a peculiar disease of the cerebral cortex. (Translated by L. Jervik and H. Greenson. 1987) *Alzheimer Disease and Associated Disorders, 1 (1)*, 3-8. Retrieved March 16, 2018 from https://www.ncbi.nlm.nih.gov/pubmed/3331112.
[8] Henry Markram, (2013). Seven challenges for neuroscience *Functional neurology, 28* (3), 145 – 151. Retrieved March 16, 2018 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3812747/.
[9] Henry Markram, (2013). Seven challenges for neuroscience. *Functional neurology, 28* (3), 145 – 151. Retrieved March 16, 2018 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3812747/.
[10] Buell, S.J., & Coleman, P. D. (1979). Dendritic growth in the aged human brain and failure of growth in senile dementia. *Science, 206* (4420), 854-856.
[11] Downs, M., & Bowers, B. (2008). Caring for people with dementia. *BMJ (formerly the British Medical Journal), 336,* 225-226.
[12] Fox, C., Lafortune, L., Boustani, M., and Brayne, C. (2013).The pros and cons of early diagnosis in dementia. *British Journal of General Practice 63*, e510-e512. Retrieved March 16, 2018 from http://bjgp.org/content/63/612/e510.
[13] Boustani, M., Peterson, B., Hanson, L., et al. (2003). Screening for dementia in primary care: a summary of the evidence for the US prevention services taskforce. *Annals of Internal Medicine, 138* (11). 927-937.

half did not believe making an early diagnosis is beneficial.[14] With so many undiagnosed, the pool of potential research participants is smaller.

Finding a cure for the many diseases of the brain is, indeed, a challenging field. While some are giving up, others are stepping forward. The Annual Adler Conference at the Salk Institute in California each year provides strong evidence that critical and important work is continuing throughout the world. Due to the generosity and thoughtfulness of John Adler, Teepa attends each year to follow that progress and to always remind the scientists of the *why* behind all their work: the people who are living with dementia. These scientists are digging deep to help those who are living with various forms of dementia because they believe there is hope for prevention and cure. Other progress has been made: differential diagnoses can now be performed to rule out various types or causes, helping patients and families make informed decisions for their life and care; scientists are coming up with risk reduction strategies targeted at some of the core contributing factors of many types of dementia; clinicians and providers - this is where PAC comes in - are developing symptom management options with environmental and human supports that are targeted to make a difference versus drugs that are not symptom specific.

Whatever is found, the PAC Team and others will continue to work hard to integrate these findings with our knowledge base, so we can help make others aware and informed.

Until there's a cure, there is PAC.

[14] Renshaw, J., Scurfield, P., Cloke, L., Orrell, M. (2001). General practitioners' views on the early diagnosis. *British Journal of General Practice, 51* (462), 37-38.