Is an increase in the Brain-derived neurotrophic factor protein a possible future treatment for Alzheimer's disease?

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ABSTRACT
Currently, there is no treatment available for the Alzheimer's disease. As the life expectancy is increasing due to greater advancements in medicine and healthcare, more and more elderly people are being diagnosed with Alzheimer's as they are living longer. However, despite the fact that research has been ongoing for many years no solution has been found to treat this disease and the efficiency of new drugs tested clinically are failing. Therefore, I present two primary possible methods to overcome this problem. Firstly, we could pioneer a preventative approach first to this problem, understand the role of BDNF production and how it will stimulate memory improvement and then secondly, use drugs as an alternative solution.

1. INTRODUCTION
1.1 Alzheimer's Disease
Alzheimer’s disease is a neurodegenerative form of dementia that will perturb a person’s competency to perform day to day activities. Currently, there are about 750,000 people in the UK that live with dementia, about 460,000, have Alzheimer’s disease [1]; most people are over the age of 65. This is caused by the development of aberrant protein ‘plaques’ (amyloid) and ‘tangles’ (neurofibrillary) in the brain [2], which intervene with how brain cells cooperate with one another and results in the evanescence of neurons (usually near the parietal and temporal lobes) and can lead to the death of brain cells. This can cause memory loss as transmission of messages within the brain becomes distorted. Currently, volunteering at Gibson's Lodge care home where the residents all have Alzheimer's has meant I have been able to gain a deeper insight into this disease and so comprehend the severity of this disease and how difficult it can be at time for the care workers to care and manage for them. A five minute conversation is difficult to maintain. The question that then arises is: How can we solve the problem associated with Alzheimer's disease? Can we stave of Alzheimer's or do we treat it?

1.2 Current Research
Current research has allowed us to approach this disease in a different angle, proving to be positive, using exercise as a means to prevent Alzheimer’s disease. Neurons that contain neurofibrillary tangles do not contain any BDNF molecules whereas neurons that contain BDNF were found to be devoid of tangles. 

By carrying out aerobic exercise, the brain structure seems to have changed, instigating the growth of blood vessels and new nerve cells. As well as the creation of neurochemicals such as the BDNF and IFG-1- that instigate growth, differentiation, survival and repair of brain cell(3). This has been a eureka moment as it has meant we can use this as an advantage to hopefully avert this disease.

What is the advantage of the stimulation and growth of BDNF as a result of exercise? Well, various different researches have demonstrated that increase levels of BDNF are essential in sustaining memory but also skilled-task performance and thus exercise will improve cognitive health. Examples of such studies are as follows: Brazilian scientists established that elderly animals that have exercised are able to perform just as well as the younger rats on experimental memory tests. Inactive elderly rats were made to run for 5 minutes several days a week for five weeks which resulted in higher levels of
BDNF molecules(4). This study therefore allows us to correlate this to human beings and elderly human patients who would be able to stimulate their own BDNF productions and therefore improve their cognition and neurogenesis. Studies in humans have also illustrated the positivity of increased levels of the BDNF molecules. Irish scientists, asked inactive male students to participate in a memory test and then asked some to carry out vigorous exercises. The memory test was then repeated. The exercised volunteers performed significantly better compared to the inactive volunteers who had rested. Moreover, blood tests demonstrated an increase in the protein BDNF, which is the biological explanation of the improvement in memory of the volunteers who had exercised as BDNF stimulates the health of nerve cells(4) and thus this is vital in developing memory and being able to recall effectively. This research has made it useful for us to consider exercise as a preventative method of the Alzheimer's disease.

1.3 Alternative Methods

When thinking about how to possibly treat Alzheimer’s disease, or in this case reduce the symptoms to slow its growth in severity –as this is a progressive disease there are certain drugs that are approved which are the cholinesterase inhibitors-Aricept, Cognex, Exelon and Razadyne. How do these medications work? These drugs increase the level of acetylcholine in the brain and inhibit the breakdown of it. Acetylcholine is a vital chemical in terms of memory, recall and learning (5). Another treatment which differs to these methods is Namenda. This is used to treat moderate-to-severe Alzheimer's disease by stimulating the brain chemical called glutamate. This is also vital in memory, recall and learning. However, the difference of this chemical compared to BDNF and Acetylcholine is that too much of it is released in brain cells in people with Alzheimer's(5) and it can damage nerve cells. However, it has been stated that 40 and 70 percent of people who have this disease only benefit from cholinesterase inhibitor treatment. Therefore, we can conclude that it is not effective for everyone who is affected by this disease (6).

Clinical trials are yet in progress and one report suggests how we can overcome the problems that mean we fail in bringing an effective successful drug. One example from many is that a model should be produced to demonstrate the progressive nature of the disease and of the drug effects from data from clinical trials whether it is positive or negative(7). Alternatively, other researches carried out by TauRux’s therapeutics seem positive and hopeful in a new drug. The current drugs that we have only seem to decrease the growth of progression of the symptoms but this drug separates the protein tangles made of tau that occlude the brain of the sufferer(8). Figure two portrays an image of how this works with description.

Recently, new drug developments have been researched with a different focal point-investigating the capability of sugars to block the activity of BACE1 protein-in the brain tissue and in the test tube—which increases amyloid in Alzheimer's disease(9).
2. DISCUSSION

2.1 Future Developments

Figure 4 illustrates the global and economic crises that we will have to face as estimated figures of people with Alzheimer's and other forms of Dementia are expected to increase. This means an effective solution will needed to be found, accepted and be of success. With more and more people being diagnosed with this disease means more and more pressures on the NHS but also more patients with lower quality of life due to Alzheimer's which causes the breakdown of communication. Therefore, if we can produce more levels of BDNF then we could possible eliminate this disease or reduce it drastically as well as other neurological diseases.

One idea is to take a preventative approach. At first, each patient should get the BDNF levels measured and according to that their own personal programme in terms of diet and exercise should be made. This would be the best, economically and natural solution. The introduction of a therapeutic strategy should be of exercise. Masses of persuasive publicity for this cause could be addressed to ensure the public is aware of the importance of exercise in terms of memory and learning but how it could prevent the long term disease of Alzheimer. If people start exercising then automatically the levels of BDFN as proven by research will increase and thus the stimulation of new nerve cells aiding cognition. 150 minutes of exercise per week could be a starting point and accessing this site [http://www.fitness.gov/](http://www.fitness.gov/) for tips and ideas would be a great start. In order for this to be successful, we'll need to think about this solution on a wide scale. Each exercise regime, the type and the duration of time spent on exercise will need to be individualized for each patient. Another factor, however, that needs to be considered is that at times vigorous exercise can cause the release of stress hormones to rapidly increase which would result in the cancellation of the BDNF positivism.

Another natural approach would be focusing on diet. Nutrients can be found that aids in producing/protecting BDNF are fish oil, acetyl-l-carnitine, blueberries and curcumin (10). This can also be publicised and incorporated into the diet. According to the levels of the BDNF in the diet, the doctor can advice how much to include in their diet. By undertaking exercise as well as changing your diet will increase BDFN as emphasised meaning it will prevent communication confusion from dysfunctional and dying neurons and therefore help defeat memory decline and Alzheimer’s (11). A change in lifestyle is essential for the future if we want to prevent Alzheimer's disease globally.

Non natural approaches for future developments would mean developing BDNF and taking it orally or being injected with it. Therefore, adjusting BDNF levels via drugs or small molecules and being able to place the BDNF directly in the hippo-campus which will promote neurogenesis. Figure 5 includes the brains of both the rat and the brain to show where the hippocampus is located and where the BDNF would have to be injected into. In terms of taking drugs orally or by injection into the body there are limitations. These are the blood-brain barrier problem, the fact that it is very short(less than
1 min) plasma half-life, and intraparenchymal penetrations. Therefore, further research would need to be carried out in order to find the best molecule to be able to enhance and modulate BDNF.

However, scientists have designed and experimented with different things to make a drug available. For example, five different tetra peptides (peptides B-1 to B-5) that all reflected 5 different regions of the BDFN were designed and tested, with the results implying that the BDFN tetra peptide are neurotrophic and would be able to adjust the BDFN signalling in a partial agonist/antagonist way, offering a therapeutic approach to neural pathologies where the BDFN levels are non regulated. That is just one example of being able to modulate BDFN with peptides. This future development would be very helpful in people who are unable to take on vigorous forms of exercise due to other health problems that may mean this method would be the best. However, this research is yet in its early stages and would need to be assessed further with more and more tests done on rats first to be able to successfully deliver the BDNF to the hippocampus to generate neurogenesis. Moreover, we cannot be too sure whether or not the BDNF after reaching the region required will enable the growth of new healthy nerve cells.

Another future development that we could consider to produce and deliver BDNF is by gene therapy. However, we would need to trail this on animals and deliver the BDFN gene to the brain of the animal. This will be delivered to the hippo-campus which is the area that is affected early on in the Alzheimer's disease, which will hopefully regenerate neurons and improve memory and skill-based learning and recall again. Figure 6 demonstrates how gene therapy typically is carried out. So, a normal gene is inserted using a vector to replace the abnormal one, but in this case we would insert BDNF because limited amounts are being produced so this method would be required to establish increased productivity of it.

What we know is that exercise is able to produce BDNF and it affects the brain behaviour but we still do not fully comprehend which parts of the brain are affected and if we do know which are then how do these effects influence thinking. Once we can overcome this, then we will be much close in accomplishing a successful treatment.

2.2 Economic and Social implications
For the suggestions of natural approaches for future development- exercising, raising more awareness, diet and nutrition. The problem that may arise for this is the agreement of willingness of various people. For instance, if we compare this suggestion with smoking, most people, if not all, are aware that smoking is harmful and is risk factors for many things but continue to smoke because the effects come into action after a long period of time and that set of thinking could apply here. People may not agree with exercising as they are not actually losing their memory just yet. Different communities may feel that they live in a deprived area or parents may feel that their parenting is being questioned. The idea of personalising each patient with their exercise and diet may mean that many will start feeling that they have no control of how they live their life. Therefore, to overcome this we can only raise awareness to emphasise on the benefits of the advice given for this solution. Another debatable question
that may arise is what is the best exercise to carry out for the brains health? This may depend on each individual and what suits them and this reflects back to the solution proposed of individualised approach for each patient.

The second treatment offered in terms of BDNF levels increasing are via tables or injections. This raises economic implications as we would need a substantial amount of funding to enable us to go ahead with the research required to make this into a success. Monitoring safety and ensuring that there are no potential side effects or ensuring that the side effects if any are minimised. So, being able to determine the safety and efficiency of the drug that will be produced and observing previous examples from history to ensure the designs are improved. We need to be able to weight up the costs spent by the NHS on drugs the patients receives who are diagnosed and the vast majority who take it compared to the money we'll spend on research in reducing large amounts of numbers. Surely, the costs for research and being able to invent a successful treatment for Alzheimer's outweighs the costs that are spent by the NHS on the patients affected. The UK spends £23 billion a year (13).

In terms of gene therapy a lot of ethical issues rise. Some patients may not agree with the idea of genetic intervention and interference in improving their memory, and thereby enhancing their abilities via this method. Moreover, if we do carry out this gene therapy then we would need to ensure that the technology is not faulty and no errors are occurred as using gene therapy will permanently affect the human gene pool. Currently, the NIH does not approve germ-line therapy in humans that is, due to so many ethical problems. Another question that can arise is that this form of technology would mean it may exclude people and the definition of 'normal' would change. This idea of 'designer' humans would be introduced differentiating people and that level of equality between people may be damaged. Furthermore, the expenditure of gene therapy is very expensive, so the question that arises here is who should be offered gene therapy, who deserves it, are we altering human traits unnecessarily and will gene therapy then only be available to the wealthy? Moreover, we are not sure about the future long term effects of using this, because of the questions arises funding for this is very difficult. However, in terms of Alzheimer's it will not set apart these people but in fact bring these patients back into the society as they will once again be able to communicate and withhold normal conversations again with increased memory as everyone else.

3. CONCLUSION
Being diagnosed with Alzheimer's disease is another way of saying your quality of life is now dead as being able to communicate becomes increasingly difficult.

The prediction of Alzheimer's disease likely to increase over the coming years means a solution is required immediately. If we are able to restore the quality of life of the patient diagnosed so that they are able to communicate and are able to recall, and a sharp memory then this will impact a lot of lives and be a success for the health care world. The easiest option first of all is to promote awareness for exercise in those who are able to carry it out as it naturally will generate BDNF therefore prompting neurogenesis. And for those who are not able to do that then the idea of using a drug to deliver the BDNF will be a key area to conduct further research in as well as assessing the safety and efficiency of the drug. It has yet not been clinically trialled on humans, it is still in its infancy but the future looks promising as clinical
trials have begun on rats. BDNF peptide seems to show a direction of progression in this field and many different scientists are pioneering different ways of treating Alzheimer's disease. Some are focusing more on how exercise affects brain behaviour and thus the production of BDNF whilst others are focusing on developing drugs by observing other things such as sugars or other chemical focus. But, focusing on exercise and BDNF seems to be the first step forward due to the possible future developments including natural approaches which will encourage most of the public to engage more in physical activities.

Although, the funding for this will be really expensive, it is still cost effective to use it on a large scale as so many patients are affected by Alzheimer's. The expectation of costs by 2038 is £50 billion (13) which is a substantial amount and is also increasing due to the increase in the number of people who are becoming diagnosed with Alzheimer's. Funding may become more easily accessible as the Alzheimer's disease is a predominant current problem that needs to be solved. I think developing the idea of Gene Therapy would pose the most ethical issues, whereas the other developments proposed would more or less be readily accepted as it brings the advantage of curing Alzheimer's disease.
Bibliography

- **Figure 1**

- **Figure 2a**

- **Figure 2b**

- **Figure 3**

- **Figure 4**

- **Figure 5**

- **Figure 6**


