How Exercise can be used in Medicine in the Treatment and Prevention of Dementia

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Pass with Merit

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ABSTRACT
Dementia is a progressive disease marked by memory disorders, which is regarded as a major public challenge worldwide that is forecast to worsen in the future. Exercise is good for both body and brain, though only recently has the extent of its benefits on the brain become clear. The link between regular exercise and the treatment or prevention of dementia was highlighted. Exercise increases blood flow and oxygen concentration in the brain as well as boosting BDNF production. This protein, BDNF, has been shown to stimulate the differentiation of brain stem cells into new brain cells and neurones thus reducing the shrinkage rate of the brain, in particular the hippocampus. The increase in the number of brain cells and neurones increases the number of possible connections for transmitting signals, which is considered the basis of learning and memory, thus counteracting the effects of dementia and natural ageing.

INTRODUCTION
It has been well known, since Roman times, that exercise is good for both body and mind. However, only recently has it become clear how regular exercise is good for the brain. Regular exercise not only improves the individual’s emotional state but current research has indicated that it could cut the risk of developing dementia and even treat those with this progressive condition.

The capability of a person to carry out basic everyday tasks, such as to think, reason and remember is often taken for granted, as such tasks are second nature to almost everyone. Yet a loss of these basic capabilities worsens the quality of life of the effected person, having a huge impact on them to the point that they may even become unrecognisable even to those closest to them. These are among the most common symptoms of the neurodegenerative disease dementia.

The word dementia does not describe a specific syndrome or disease but rather the general symptoms that a number of diseases may display. It originates from the Latin word ‘dementem’ which consists of two parts ‘de’, meaning ‘apart’, and ‘mentem’ whose root word, ‘mens’, means ‘mind’ (Nordqvist 2009).

Dementia according to Online Oxford Dictionary can be defined as:

‘A chronic or persistent disorder of the mental processes caused by brain disease or injury and marked by memory disorders, personality changes, and impaired reasoning’

Dementia is a progressive disease meaning that its symptoms will persist over a long period of time and the condition of the patient is likely to deteriorate at a rate that is far higher than that that can be expected from normal ageing. There are many different types of dementia each of which has its own specific causes and set of symptoms. However, dementia is mainly caused by the death or damage of brain tissue, which in turn affects the transmission of the chemical messages across neurones.

All feelings, thoughts and memories are a consequence of signals passing through nerve cells called neurones in the brain. The brain is made of more than 100 billion neurones that communicate with each other by transmitting chemicals called neurotransmitters. A neurone is made up of three parts: a cell body that contains the cell’s organelles, dendrites which have branched receptors that receive and
initiate the electrical impulses meaning they transmit and receive messages from other neurones, and
finally, there is the axon which relays the electrical impulses. Between the axon and dendrite ends there
is a small gap called a synapse. Neurotransmitters are used to transfer the electrical impulses across the
synapse hence regulating the electrical impulses. At the axon end neurotransmitters are released from
their vesicles crossing the synaptic gap where they bind to the receptors located on the dendrites.
(Boeree, 2009) These signals are fundamental to the processes of learning and recalling new and old
information. There are many types of neurotransmitters, of which eighty per cent of those found in the
brain involve two key neurotransmitters: Glutamate and Gamma-Aminobutyric Acid (GABA).
Glutamate is an excitatory chemical neurotransmitter in the brain. It works by starting a cascade of
signals between the neurones meaning that more connections are generated which is key to being able
to process more information. GABA on the other hand is an inhibitory chemical neurotransmitter that
works in contrast to Glutamate by preventing the over excitation of neurones. This therefore implies
that having more glutamate and glutamate receptors, such as N-methyl-D-aspartate (NMDA), can in
fact help with learning and memory.

A study, by the scientist Susumu Tonegawa, on mice that lacked the NMDA receptor gene showed that
without these receptors mice could not memorise a simple task called the ‘water maze’. Such studies
have highlighted the importance of Glutamate and its NMDA receptors in the learning process and
have provided evidence that the presence of this neurotransmitter could possibly be adapted in the
context of dementia treatment. (Howard Hughes Medical Institute web pages)

An increase in such neurotransmitters and receptor numbers is indirectly linked to the presence of a
protein called Brain-Derived Neurotrophic Factor (BDNF). This protein, which is thought to help with
mental sharpness, learning and memory, acts by increasing the endurance of neurones and encouraging
their increased growth and differentiation from stem cells. This in return aids learning and memory as
more connections can be forged in the brain. (wikipedia.org) With current research showing that
exercise can help with the secretion of BDNF, this brings forward new ways in which exercise can in
fact be used in the treatment of neurodegenerative diseases such as dementia.

Dementia is a major public challenge for the 21st century. According to Alzheimer Disease
International (2008) there are approximately 30 million people with dementia worldwide and
this figure is expected to increase to 100 million by 2050. In Europe, it is estimated that there
are more than 6 million people with dementia. A recent report ‘Dementia 2010’ revealed that
the cost of dementia in the UK is twice, three and four times as much as that of cancers, heart
disease and strokes, respectively (Luengo-Fernandez et al. 2010). These figures highlight the
vast scale at which dementia affects people’s lives in today’s society and hence emphasises the
importance of finding effective treatments to both relieve symptoms and help in its future
prevention.

Possible types of treatment being researched range from using drugs to changing lifestyle at
different ages. Although some cognitive enhancers and anti-dementia drugs are being used,
they do not provide a cure but merely slow down the onset of the deterioration of the
symptoms. This has led to the need for current medical research, which has in turn highlighted
the possible link between regular exercise and prevention or delayed onset of dementia which will be explored further in this article.

DISCUSSION
There are many symptoms that dementia sufferers may show, though the severity and combinations of these symptoms differ from one to another. The general symptoms that are more frequently exhibited are:

- Memory loss, predominantly short-term memory.
- Moodiness due to the damage of parts of the brain that control emotion
- Communication problems

The term dementia mainly encompasses four different conditions or diseases. Each of them has its own specific symptoms, causes and stages of progression. These are according to the Alzheimer's Society:

- Alzheimer’s Disease
- Vascular Dementia
- Dementia with Lewy bodies
- Fronto-temporal Dementia

Alzheimer’s disease is the most common form of dementia and is caused by the damage or death of brain cells leading to changes in the chemistry and structure of the brain. The death of many cells results in a lower than average cell count in the brain and therefore leads to fewer connections and communication between the cells overall as the neurotransmitters decrease in amount. Consequently, the brain shrinks due to the loss of nerve cells and fibres. When samples of brain cells of an Alzheimer’s suffer are examined further by microscope, tiny plaques and tangles can be observed and tangles are also seen forming in the brain. The plaques are clumps of a protein called beta-amyloid and their presence is what damages and destroys the brain cells while interfering with cell-to-cell communication. The tangles are protein strands that damage the transport system of the brain by forming abnormal pathways (Mayo Clinic 2011).

Vascular dementia is also caused by a loss of brain cells, though this occurs due to a failure in blood supply to the brain. Brain cells are constantly respiring and hence in need of a constantly good supply of oxygen to accommodate this. A lack of oxygen, even for a short period of time, can cause these cells to stop respiring and die. This can occur suddenly via a stroke or more gradually through several small strokes. Due to this, factors such as high blood pressure, high cholesterol levels, cardiovascular problems, smoking and a lack of exercise increase the risk of vascular dementia.
Dementia with Lewy bodies gets its name from the spherical protein deposits that form inside nerve cells. These protein deposits damage the nerve cells which they occupy and therefore lead to degeneration of brain tissue.

In Fronto-temporal dementia, the degeneration of brain cells is generally centred on the front part of the brain meaning that with this type of dementia, personality and behavioural changes are observed first with changes in memory at a later stage as the disease progresses.

Though these are the four main conditions that lead to dementia, there are also a number of other conditions that may lead to the development of dementia. These include diseases such as Parkinson’s disease, HIV/AIDS and Huntington’s disease amongst others. There are also theories that suggest that there may be a genetic element to the development of dementia. Genes determine protein structures within the body, hence this means that certain genes may increase or decrease the susceptibility of an individual to a disease or condition. However, due to the fact that many different genes can interact together, the effect that the environment has and the complicated patterns of inheritance, it is extremely difficult to identify the genes that maybe responsible for or increase the susceptibility of developing dementia.

The vast majority of dementia cases are incurable by modern medicine as treatment is mainly aimed at controlling or decreasing the rate of deterioration of the patient. Drugs are used to help treat the symptoms of dementia as well as decrease its likelihood of occurring in later life. These drugs are commonly prescribed by doctors mainly to treat Alzheimer’s disease though they may be used to counteract the effects of other forms of dementia such as vascular dementia. There is also evidence showing that drugs used for the treatment of other conditions may also be effective at treating dementia or slowing its progress. An example of this would be Selegiline, which is used in the treatment of the early stages of Parkinson’s disease (Nordqvist 2009). This has been shown to slow down the progress of dementia. Scientists are carrying out research into such drugs with the hope that common drugs may one day be used to treat or prevent dementia. Correlations between a number of drugs and a reduced chance of dementia have been found though whether or not they work is yet to be proven. Such drugs, in addition to Selegiline, include beta-blockers, diabetes medication and drugs for psoriasis (Nordqvist 2009). All these drugs though not prescribed for dementia have been found to lower the risk of it occurring in later life.

Other than using drugs to counteract dementia, there are also a number of simple lifestyle choices, habits or abilities, which have been shown to reduce the likelihood of dementia. One such ability is being bilingual. A study in Canada showed that being bilingual, speaking both English and French, delayed the onset of dementia by an average of 4 years. Many such characteristics that people may possess have been linked to a reduction in the chance of dementia. Simple things such as diet, mental and social activity, smoking, alcohol consumption and exercise have been shown to have a significant impact on the risk of developing dementia in later life (Nordqvist 2009).
A number of other therapies have also been found to help. Cognitive and behavioural therapies as well as music therapy have been found to decrease the symptoms of dementia. As research into the genetic aspect of dementia progresses, it may become possible to treat or prevent the onset of dementia to an extent by using gene therapies. However, these types of treatments are very complicated and raise ethical issues. A vector is needed to transport the gene into the cell, which can be dangerous and due to the complicated nature of gene interactions, results cannot be fully predicted prior to the treatment.

It is not a mere coincidence that regular exercise and a healthy diet are often adopted together as common practice. Researchers found that exercising regularly helps to enhance the brain's resources for functions like inhibitory control; this eases the temptations for unhealthy food and instead promotes healthy meal options (Mercola 2012a). Healthy eating and taking food supplements such as vitamins and additives is also said to reduce the effect of dementia by providing alternatives to drugs and medications and this habit aids dealing with mental health problems. (Alzheimer Association, 2013).

Physical exercise has been shown to have a significant impact on the risk of developing dementia. It is well known that regular exercise is good for the body in general; it is a major factor for achieving a healthy and longer life expectancy and reduces the risk of developing chronic diseases. Regular physical exercise decreases stress levels, increases the levels of endorphins in the blood and improves blood pumping and circulation. Brain cells are constantly respiring and are hence in need of a steadily good supply of oxygen to accommodate this need. Evidence suggests exercise may directly benefit brain cells by increasing blood flow and hence oxygen concentration in the brain. This increased supply of oxygen appears to improve memory and learning abilities and helps lower the risk of some types of dementia (Rattue 2012). It is a known fact that age is associated with memory loss. However, it has been proven that aerobic exercises have different effects on the brain and memory depending on the exerciser's age. Exercising as an adolescent had longer lasting effects compared to carrying out the same exercise for the same duration as an adult. A team of scientists in Psychological and Brain Sciences have identified a gene that seems to regulate to what degree exercise provides a beneficial effect (Rattue 2012). Exercise sharpens thinking and supports problem solving by boosting the production of ‘BDNF, which has been found to recycle and rejuvenate brain and muscle tissue by stimulating the differentiation of stem cells. This process creates new brain cells and hence in doing so counteracts the natural degeneration of the brain which is a cause of dementia.

It is thought that exercise helps delay age-associated memory loss. The hippocampus, a small area of the brain, which plays an essential role in learning and memory, shrinks as we get older. Without a hippocampus, one would be unable to form new memories meaning that only old ones would be remembered (Trudeau 2011). However, profound memory loss, such as that exhibited by dementia patients, is also caused by accelerated hippocampus shrinking. The major chemical change in the hippocampus during aerobic exercise is an increase in the
concentration of BDNF, which nourishes new connections between neurones (Figure 1) through the differentiation of brain stem cells. This indicates that regeneration is not impossible for brain cells contrasting what was previously thought. Exercise reduces the shrinkage rate of the hippocampus (Trudeau 2011) as well as stimulating nerve growth factors (Lawrence 2012).

Extensive research towards understanding the neurobiological bases and their benefits on humans suggests that exercise could have benefits for overall health and cognitive function. Exercise can increase the levels of BDNF and other growth factors (Swardfager et al., 2011), which stimulate neurogenesis, increase resistance to brain damage and improve learning and mental performance. Hence, this may delay or even prevent dementia at a later age. Therefore, exercise is a simple means to maintain brain function and promote brain plasticity (Cotman & Berchtold, 2002).

Figure. 1. Characteristics of brain-derived neurotrophic factor (BDNF) that make it a natural candidate to mediate the benefits of exercise on brain health. (a) BDNF is transported to synapses; BDNF mRNA and protein levels increase in an activity-dependent manner. (b) Released BDNF binds to its receptor (TrkB) to modify transmitter release and postsynaptic sensitivity. (after: Cotman & Berchtold, 2002)
Physical exercise helps to build a brain that not only resists shrinkage, but also increases cognitive abilities. One of the most exciting aspects of recent research is that regular exercise actually increases the size of the brain as it triggers the creation of new neurones in the hippocampus. Regular exercise seems to initiate the expression of the BDNF gene, increasing BDNF synthesis which in turn stimulates the growth and production of new brain cells and neurones from stem cells. Such an increase in the number of brain cells and neurones increases the number of possible connections for transmitting signals between neurones, which is considered the basis of learning and memory. Hence, the effect of exercise on the brain is not only generative, but also regenerative (Siegfried, 2012).

During exercise, nerve cells release BDNF proteins. BDNF also triggers numerous other chemicals that promote neural health. BDNF also expresses itself in the neuro-muscular system protecting neuro-motors from degradation. BDNF’s activity in both muscles and brain explain why a physical workout can have such a beneficial impact on the brain tissue. It essentially helps to prevent brain decay as much as it prevents and reverses age-related muscle decay. However, sugar suppresses BDNF synthesis, which helps explain why a low-sugar diet in combination with regular exercise is effective for protecting memory and treating depression as well as dementia. (Mercola 2012b)

According to a research published in Elsevier’s journal Brain, Behavior, and Immunity by a team of researchers, regular exercise could help prevent brain damage associated with neurodegenerative diseases like Alzheimer’s (Funk et al. 2011). Professor Jean Harry leading this research at the National Institute of Environmental Health Sciences in the United States stated that: “Exercise allows the brain to rapidly produce chemicals that prevent damaging inflammation” and hence, helps to “develop a therapeutic approach for early intervention in preventing damage to the brain”.

Another possible cure or treatment for dementia is through the use of stem cells. There has been much research into this domain for the treatment of many different conditions though this type of treatment does raise a variety of ethical issues, most of which revolves around the use of embryonic stem cells (Elliott 2013), and whether or not the embryos used are regarded as human beings. Theoretically, there could be the possibility of injecting brain stem cells into the patient’s brain, which would start to differentiate creating more brain cells and neurones. This will increase the overall number of cells and hence possible connections in the brain counteracting the effects that ageing has and possibly even that of dementia. As those lost cells are gradually replaced, the capacity of the patient, their memory and other problems they may have developed should theoretically start to reverse. However, further more specified research must be carried out in relation to these possibilities to ensure their safety and effectiveness. Such methods have been used to counter the effects of conditions such as Huntington’s disease and Parkinson’s disease, where they are used to replace degenerated neurones and nerve cells thus re-establishing lost connections. Due to such breakthroughs, scientists believe
that such treatments have the possibility of treating a wide variety of neurodegenerative diseases amongst which is dementia (Tiantan Puhua. 2013).

Due to the number beneficial effects that BDNF can have on the body and especially the brain, artificial synthesis of this protein and its use as a supplement to mimic its action in nature can be of extreme benefit to dementia patients. However, research has shown that BDNF does not cause these effects alone, but rather works as part of a cascade of proteins, hence further more precise research must be carried out to identify the other proteins in the cascade and the effects that supplementation of just BDNF may have. Gene therapy may be used to initiate the natural synthesis of BDNF, though the gene responsible for its production must first be identified, isolated, its corresponding mRNA synthesised and then delivered to the correct target cells for its transcription.
CONCLUSION
To conclude, there is significant evidence to suggest a link between regular exercise and mental health. Though such a link has been known of for a long time, only recently has the extent of this link come to light. Through various scientific research, links have been drawn as to the more specific effects that exercise has on the brain. Correlations between the abundance of certain chemicals and the amount of exercise done have been found. The most significant of which is the link with the protein, BDNF. This protein has been linked to a wide range of different effects on the brain, including the decrease in the amount brain shrinkage, the stimulation of neurogenesis, increase in the endurance of neurones in the brain and the decrease in the susceptibility of the brain cells to damage. However, though these links are clear and suggest that exercise would be an appropriate treatment for dementia, due to the hugely diverse nature of dementia and the large number of causes, it is highly unlikely that exercise, on its own, is the cure. Nonetheless, it is certain from the findings above that exercise will play some role in the alleviation of dementia’s symptoms as well as its prevention, such as the delaying of its onset.
REFERENCES

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