As growing every year. it is estimated that

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Asthe elderly population in Canada continues to grow, so does the incidence ofmany age-related health problems. Alzheimer’s disease (AD) is among these, oneof immense importance.

AD is a chronic neurodegenerative disease characterizedby memory loss and gradual cognitive impairment beyond what is expected fromnormal aging. It is one of the most common forms of dementia, having aprevalence of 60-70% of all dementia cases1. Thereis still much to learn about this disease as the exact biological cause isstill not known. However, there are several hypotheses to how the damage iscaused in the brain leading to the cognitive impairment.

The primary hypothesisis on the accumulation of amyloid-beta and Tau proteins, which are thought toform plaques and tangles in the brain2-3. It is unclear to the exactroles that these play in the disease; however, they are found in significantamounts in autopsies of people with AD. It is believed that these plaques andtangles can block communication signals between neurons, thus leading to neurodegenerationor death of neurons. This is what is believed to cause the memory loss, and theother symptoms of Alzheimer’s disease. InCanada alone, 564, 000 people live with dementia with the numbers growing everyyear. It is estimated that by 2031, the numbers will almost double, affectingup to 937, 000 Canadians4. The growing effect of the disease has notonly affected the people with the disease but also put and huge financial drainon the Canadian health care system and the thousands of caregivers.

In 2016alone, the combined costs of treatment and care are estimated to be up to $10. 4billion4. A large proportion of the cost is toward pharmacologicaltreatments.

The search continues to find a cure for Alzheimer’s as therecurrently exists none that can stop or reverse the progression of the disease. Research has been focusing on multiple viable treatment options to relievesigns and symptoms, one of the more popular focus being pharmacological. Howeveradditional to the problem with economic cost, medicational treatments commonlyhave multiple unpleasant and unwanted side effects. Thus this gives incentivesfor research to move outside of the medicinal regime and look at differentnon-traditional routes such as prescription of a certain amount of Physical Exercise(PE). Currently, there is a staggering growth of research studies looking into exercise as aviable treatment. As seen in Figure 1, the number of publications on PubMed onthe topic of “ Exercise and Alzheimer’s disease” has been growing exponentially, research on this topic has almost doubled in the past 10 years. There have beenalmost 300 publications on this topic in 2017 alone. This just emphasizes thatmore and more resources are used to look into this non-traditional treatment asan option for treating AD.

Figure1: Publications on Alzheimer’s and Exercise over the Years IncreasedPE has been long proven to help with both mental and physical health of peopleof all ages and health status5. It does not have the unpleasantside-effects like many common pharmacological options and may prove to be quitea viable option of treatment for AD. Previous data from several studies,

bothanimal and epidemiologic, has shown that physical exercise has improved thequality of life of people living with Alzheimer’s and even improved the qualityof life of their family and caregivers.

Though several studies were conductedin this area, there is a lack of consensus regarding to exact mechanisms to howexercise helps with cognitive impairment in people with AD. It is also unclearto how much physical activity, what kind, and at what intensity is optimal todecrease the cognitive decline and improve the lives of people affected with AD. The goal of this research paper is to conduct a literature review to look at bothbasic science research and epidemiological research to synthesise data on thepossible mechanisms of how physical activity improves cognitive abilities inpeople with Alzheimer’s disease and to summarize the results of the clinicalstudies to create a guideline/recommendation for physical activity in peoplewith AD. Mechanisms of interaction betweenphysical exercise and cognitive decline in Alzheimer’s: Voluntaryexercise has been shown to reduce amyloid-beta amounts in transgenic mice6.

Results such as these are exciting as they offer a simple relationship betweena cause and the effect of reducing Alzheimer’s plaques in the brain. There isconsensus that exercise can reduce the symptoms and determents of AD butunfortunately, the underlying reasons why exercise may provide a biologicalcausality for plaque clearance is unknown. However, there are several hypothesesof the inverse relationship of the two. Figure 2 shows a chart summary of the severalhypotheses of potential mechanisms that are going to be further discussed thisresearch paper. Figure2: Summary of

Mechanisms Exercise and Growth Factors: Oneplausible hypothesis is that exercise has a positive effect on activatinggrowth factors such as insulin-like growth factor 1 (IGF-1), vascularendothelial growth factor (VEGF), and brain-derived neurotrophic factor (BDNF).

The exact pathways of activating these growth factors through PE is unclear, however studies have shown promising positive correlations between the two. InAD, cells in the hippocampus, which are integral to learning and memory, undergo neuronal atrophy. The BDNF family of signaling molecules are elusivefor their roles in neuron regulation, growth, and especially memory formation7. In patients with Alzheimer's disease, there is a down-regulation of the genesthat produce BDNF in the hippocampus7. Simply, researchers havefound that exercise increases the levels of BDNF produced in the brain forlater cell signaling during body repair7. This may counterbalancethe loss of BDNF and memory function from Alzheimer's disease. BDNF also activatestropomyosin-related kinase B (trkB) receptors on oligodendrocyte precursorcells8-9. This promotes the formation of new oligodendrocytes to initiatethe myelination process in nerve cells.

Though increased myelination, signaltransmission efficiency is improved between nerve cells which can lead tobetter memory functions in the hypothalamus8-9. IGF-1, like BDNF, are also found in lower than normal levels in the AD brain and the reductionin the expression level of this growth factor has been associated with AD neuropathology. There is also evidence IGF-1 has a potential protective effect against AD11-13. Thusby increasing

cerebral IGF-1 levels through PE, the AD brain will bepotentially subjected to less neuropathology.

Neurogenesisis quite difficult to measure in humans; however, rat studies have shown improveshippocampal neurogenesis through PE14. By inducing both BDNF andgrowth factor expression in the brain, PE can significantly enhanceneuroplasticity and neurogenesis, and therefore lead to increased hippocampalfunction. Improvement of Vascular Function: Aboutone-third of the AD cases are complicated with vascular pathologies leading toa synergistic effect on cognitive decline16-17. Therefore, another viablehypothesis that is considered by many researchers is that PE causes animprovement in cerebral vascular functioning and perfusion in the brain; thismeans that there is an increase in cerebral blood flow to supply to the neuronsleading to improved neurogenesis in certain brain areas. Both animal and humanstudies have shown that there is a significant increase in brain perfusion andangiogenesis within just few weeks of aerobic training17.

Thebeneficial effects on cerebral blood flow have been associated with the reductionof cerebrovascular and endothelial dysfunction pathophysiology in people withAD. This effect is due predicted to be due to the activation of nitric oxide(NO) which is derived from endothelial NO synthase (eNOS). NO plays a pivotalrole in vascular tone, blood pressure, and vascular homeostasis18-19. AD pathology causes a deterioration of NO homeostasis leading to hypoxia Thusby increasing NO, vascular reserves in the brain will improve leading to maintenanceof neuronal plasticity. Moreover, Vascular endothelial growth factor (VEGF) isupregulated with exercise20-21.

VEGFproduction is triggered by hypoxia which happens during aerobic activities suchas PE17. These vascular growth factors can act on the endothelialcells lining the wall of the blood vessels in the brain triggering them todivide and produce new blood vessels resulting in better perfusion20-22. Through either two of the mechanisms mentioned, brain perfusion will increasehaving the potential to decrease certain AD pathologies related to vascularfunctions.

AmyloidPlaque Deposition and Neuroinflammation: Onekey characteristic of AD is the formation of amyloid-beta plaques in thecerebral cortex and hippocampus. Several research has shown reduction of plaquedeposition in AD mice who undergo aerobic exercise23-24. This initself can help improve pathologies in individuals with Alzheimer's. Inflammationis usually a protective response; however, unmanaged and prolonged inflammationcan lead to multiple complications and pathologies, and most importantly, increased redox stress upon cells. In people with AD, there is an increasedamount of amyloid-beta deposits which are able to activate astrocytes whichturn will release of proinflammatory mediators including TNF-a, and interleukinIL-1b25.

Since the amyloid-beta aggregates and cannot be cleared, proinflammatory mediators will be constantly expressed leading to prolongedinflammation in the brain which can have detrimental effects causing neuralatrophy. If inflammation is somehow reduced in the brain, less damage will becaused by the amyloid-beta deposits45. Anotherhypothesized mechanism is that exercise is believed to decrease the amount ofinflammation in the brain.

One possibility is that exercise increases clearanceof amyloid-beta, consequentially, there will be less amyloid-beta to enter theastrocytes and therefore less proinflammatory mediators being released25. Evidence for the reduction of cerebral inflammation is found in a transgenicAlzheimer's mouse models sedentary mice had a higher hippocampal expression ofproinflammatory interleukins IL-1b and TNF-a, and reduced levels of anti-inflammatorymarkers such as interferon-gamma (IFN-g) and chemokine ligand 3. When the ADmice were put through an exercise regime of swimming, they were shown to have alower periphery expression of inflammatory markers than sedentary mice26-27. Clinical Applications of PE in peoplewith Alzheimer's: Thebasic science research showed quite consistent results; however, theexperiments were all done in a controlled setting. For more applicableevidence, I reviewed several clinical trials that used PE as a treatment forAlzheimer's disease. Looking into several prospective studies, there has beenquite consistent evidence that increase PE had beneficial outcomes for peoplewith Alzheimer's. Hernández et al. conducted a systematic review in this topicincluding 15 different RCTs28.

Thirteen of the included studies hadpositive results and they were able to conclude that the practice of physicalexercise could present significant results for the improved functionality andperformance of daily life activities, improvement in functional capacitycomponents (flexibility, agility, balance, strength), and improvement in certaincognitive components such as sustained attention, visual memory, and frontalcognitive function in people with mild to severe AD. The clinical studies lookedat different kinds of outcomes including: physical function, cognitive functions, career burden,

self-care and mobility. Forthis research paper, I will mainly be focusing on the outcome of improvementson cognitive functions.

Theseveral studies I looked at had various ways of measuring cognition and theyalso had different conclusions on the benefits of PE. Vreugdenhil et al. conducted a randomized controlled trial (RCT) on small community of people withAlzheimer's. Their findings had a positive result (p <0. 001) showing that at 4-monthsfollow-up, the individuals who were randomized to exercise had better improvementin cognition, which was measured by Mini Mental State Examination scores, compared to those in the controlled group29. Öhman H et al. on theother hand, found only partial improvements in cognitive functions; an RCT of 210individuals with AD was conducted measuring cognitive functions through ClockDrawing Test (CDT), Verbal Fluency (VF), Clinical Dementia Rating (CDR), andMini-Mental State Examination (MMSE). Groups allocated to the exercise regimewas able to significantly improve (p= 0.

03) than those in the control group atthe Clock Drawing Test. A positive effect was only observed in the CDT and wasnot observed in the other domains of cognition measured30. Morris etal in their RCT concluded that there was no clear effect of intervention (PE) onprimary outcome measured including Memory and Executive Function. However theydid find a correlation between cardiorespiratory fitness between change inmemory performance and bilateral hippocampal volume31. This matches withthe findings of a systematic review done by Angevaren et al. where they foundthat aerobic exercise with an intensity improves cardiorespiratory

fitnesswhich can lead to beneficial for cognitive functions in healthy older people32. Thoughthese studies had a variety of different conclusions, it is still prettyconsistent that exercise has the potential to aid in cognitive functions. Thesestudies do have their limitations because just like basic science studies, theyare in a more controlled setting as the long-term adherence to frequent PE isnot measured; the studies with the positive effects also were not able toreport if the benefits were sustained after the study concluded.

Moreover, there are very few studies withlarge sample sizes on this topic. . FinalizedExercise Recommendation: Evenwith the limitations of both basic science and clinical studies, there is quiteconvincing evidence that aerobic exercise does help people with Alzheimer’sdisease. Using the studies that I have read up on, I came up with a recommendedexercise recommendation. Recommendations for Exercise: 150 minutes weekly of moderate exercise (add in resistance training for additional benefits) Exercises can include: walking, jogging, biking, swimming, simple exercise programs Start off with low-moderate intensity to promote adherance Physicians should take into account their individual patients to make sure that each of them gets the appropriate exercise regime due to their potential comorbidities. At least 6 months of PE is recommended to see results 150minutes weekly of moderate-intense exercise (add in resistance training foradditional benefitsInmultiple studies of RCT’s I looked at, a majority of them did show animprovement of by just introducing the intervention of 150 minutes of aerobicexercise per week35-37.

They are found to be cognitively protective andassociated with increased hippocampal volume plus improved spatial memory. Surprisingly, this is also similar to the recommendation of the WHO, which advises “ Toimprove overall cardiovascular health, we suggest at least 150 minutes per weekof moderate exercise or 75 minutes per week of vigorous exercise” 38. Aerobicexercise implies training that elevates heart rate and increases Vo2. Thestudies reviewed used multiple different exercises to achieve this, the mostcommon ones being walking, running, walking and resistance training 29-31, 33-34, 39. Oneof the RCTs even used a Home Support Exercise Program which is made for frailelderly people which has been tested for both feasibility and safety29. All these were able to show effective resultsin improving cognitive functions in people with Alzheimer’s. Startoff with low-moderate intensity to promote adherence: Wehave to take into account practicality as well as many of these clinicalstudies did not follow-up on patients after their completion and thus it isdifficult to tell if the individuals stuck to the regime.

By prescribing aninitial low-moderate intensity, it promotes practicality and adherence at thebeginning of the program40. Moreover, high, intensive aerobicexercises can lead to certain adverse effects such as orthopedic injuries, increase fall risk, and provoke acute coronary syndromes. Atleast 6 months of PE is recommended to see resultsStudieswith intervention (PE) lasting 6 months and more had higher chances ofimprovement in cognitive functions41-42.

There is also evidence thatshort term increase of aerobic exercise did not benefit the individual inseveral studies43-44. Several studies that only introduced a short-termexercise regime (<12 weeks) not enough to improve cognitive impairment inindividuals with Alzheimer's. Thus the exercise can't just be for short-termbut a life style change. Physiciansshould take into account their individual patients to make sure that each ofthem gets the appropriate exercise regime due to their potential comorbidities. Thus, physicians should help patients select exercise programs compatible with theircapabilities and cardiopulmonary status.

Thus doctors should assess theirpatients for risk factors before recommending certain exercise practices. Conclusion: Aslooked at several pathways and basic science studies, there are convincingevidence that exercise can promote a better cognitive function in people withAlzheimer’s. The human research studies had many different conclusions but thismay be due to the fact that they all had different measurements to look atcognition functions and the studies themselves have limits due to the smallsample sizes. Published systematic reviews of these studies has shown a small butnonetheless significant directional results towards the PE allocated groups. Moreresearch is still needed to have a more definitive result with larger samplesizes. A recommendation of ongoing, moderate-intensity physical exercise shouldstill be considered as an option for individuals with Alzheimer’s as regularaerobic exercise has multiple potential benefits that are not just limited toimprovements in cognitive functions.