EFFECTIVENESS OF CLINICAL DRUG TREATMENTS FOR ALZHEIMER'S DISEASE IN SLOWING PROGRESSION OF MEMORY LOSS & COGNITIVE FUNCTION LOSS

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ABSTRACT: The effectiveness of Alzheimer's Disease drugs is crucial to knowing what drugs can be used to treat Alzheimer's Disease and which ones do not. Currently, Aricept, Ebixa, Exelon and Lamivudine are the drugs used to slow the progression of Alzheimer's Disease. These drugs are used to slow the symptoms of memory loss and cognitive function loss. In this proposal, I will be investigating the effectiveness of these drugs in slowing the progression of memory loss and cognitive function loss through administering memory tests, cognitive tests, surveys, PET scans and CT scans to Alzheimer Disease patients. The drugs tested will be considered effective if there is evidence of a slow in memory loss and cognitive function loss.

Background & Introduction

Alzheimer's Disease also known as AD, is a neurological disease that diminishes the brain's ability to memorize and process daily tasks. The first case of AD was identified in 1901 from Dr. Alois Alzheimer in a woman named Auguste Deter (Hippius et. al, 2003). This woman later died in 1906 with one of the classic symptoms of memory loss. The doctor conducted an autopsy of the deceased and found she had brain plaques and neurofibrillary tangles, which are classic indicators of AD (Hippius et. al, 2003). In 1906, Dr. Alzheimer's findings go public and the term "Alzheimer's Disease" becomes the term used to describe said disease. AD affects a person's social and behavioral skills as the disease progresses. AD has no cure because no drug has been able to reverse the brain damage done at the neuron level. Research into treatment for AD is expensive and scientists still don't know what causes AD. However, there are medications currently being used to deal with the symptoms of the disease. In the United States alone, 5.8 million people have AD and deaths due to AD have increased 145% (Alzheimer's Association, 2019). It is important that scientists find effective treatments for AD to decrease the symptoms and to decrease the medical costs associated with AD.

AD patients tend to live between 4 and 20 years after their diagnosis. The disease has four stages and is mostly common in elderly adults. Stage 1 of AD, known as the pre-dementia stage, has the symptoms of short-term memory loss, decreased attention span and decreased awareness. This stage lasts seven years and affects the Medial Temporal Lobe of the brain, which is responsible for memory (McMaster University, 2018). Stage 2 of AD, known as the mild stage, has the symptoms of learning impairment, language difficulties and poor sense of direction. This stage lasts two years and affects the Temporal Lobe, which is responsible for language, hearing, facial recognition and visual processing. It also affects the Parietal Lobe, which is responsible for processing and interpreting sensory information, visual information, language and mathematics (McMaster University, 2018). Stage 3 of AD, known as the moderate stage, has the symptoms of long-term memory loss, loss of urinary and bowel control, behavioral changes, short attention span and poor judgment skills. This stage lasts two years and affects the Frontal Lobe of the brain, which is responsible for controlling emotions, memory, language, judgement, sexual behaviors and problem-solving skills (McMaster University, 2018). Stage 4 of AD, known as the

severe stage, is the stage in which a patient loses the ability to feed themselves, loses speech function, has problems with vision and eventually dies. This stage lasts three years and affects the Occipital Lobe of the brain, which is responsible for processing visual information such as facial recognition, memory formation and depth perception (McMaster University, 2018).

A person who has AD will start developing plaques and tangled bundles of fibers that will later cause loss of neuron transmission. Neuron transmission is vital to the brain because neurons transmit signals from the brain to other parts of the body and is important, when it comes making memories. If neuron transmission stops then body parts lose functionality, signals and nutrients for systems. AD begins in the hippocampus, which is the part of the brain responsible for short-term and long-term memories. As the disease progresses, the brain shrinks to the point where the brain has irreversible damage.

AD research is currently looking at how to slow the progression of the disease. The common drugs used to treat the symptoms of AD are Aricept, Ebixa, Exelon and Lamivudine. All of these drugs are FDA approved. When it comes to AD, drug effectiveness is key to slowing the progression of the disease. In this proposal, we will be comparing the effectiveness of AD drugs Aricept, Exelon, Ebixa and Lamivudine in slowing the symptoms of memory loss and cognitive function loss in the brain. Each drug's effectiveness will be tested through memory tests, brain scans and surveys. These tests are used to see what parts of the brain are affected by the drugs, what can the patients remember, how are they affected socially and behaviorally from these drugs and how has the treatment affected them overall.

When it comes to the drug treatments Aricept, Exelon, Ebixa and Lamivudine each of them performs different roles for people with AD. Aricept, also known as Donepezil, is a drug used to treat dementia. The drug acts as an enzyme blocker in the brain by restoring the balance of neurotransmitters (WebMD, 2019). This is important because Alzheimer's Disease is the degradation of neurons and loss of neuro transmission. Without neurotransmitters being stimulated, messages between neurons would be lost and brain function for various jobs would decrease. This drug has been shown to be effective in slowing the progression of the disease, when it comes to memory loss (Graber et. al, 2011). The second drug we will be investigating in this proposal is Exelon. Exelon commonly known as Rivastigmine or Rivastigmine Tartrate, is a cholinesterase inhibitor that prevents the degradation of neurotransmitter acetylcholine (Flavell, 2019). This neurotransmitter is responsible for memory, motivation, cognition, attention and arousal. This drug when paired with Ebixa and individually has been proven effective in slowing the symptoms of memory loss and cognitive function loss in people, who have AD in the two studies (Frolich et. al, 2012) and (Onor et. al, 2007).

The third drug that'll be investigated in the proposal is Ebixa. Ebixa commonly known as Memantine or Namenda, is a treatment for patients with moderate to severe forms of Alzheimer's Disease. This drug acts as a blocker for N-methyl-D-aspartate (NMDA) receptors that neurotransmitter glutamates bind to (Alzheimer Society of Canada, 2008). As this drug blocks NMDA receptors, it increases neurotransmission which decreases complications associated with AD. This drug in the two studies (Molino et. al, 2013) and (Rountree et. al, 2013) was shown to be effective in treating people with AD, when it was paired with Aricept and when Ebixa was tested individually up against other treatments. The fourth drug that'll be investigated in the proposal is Lamivudine. Lamivudine is a known antiretroviral drug used in HIV treatment. However, Lamivudine has been shown to have significant effectiveness on patients with AD in the area of epigenetic targeting (Chatterjee et. al, 2018). Epigenetic targeting is a drug that targets gene expression of a disease without altering the DNA of the individual.

Hypothesis & Research Question

Based on information provided from each drug, if AD patients report or show signs of a slowing in memory loss and cognitive function loss then the drug is effective in treating people who have AD because it showed a significant effect in the brain of individuals with AD. If the drug passes the memory tests, shows significant signs on a CT scan and PET scan, or shows positive correlation in survey data then the drug is effective in slowing the symptoms of memory loss and cognitive function loss in people with AD. We will select 1,000 people with AD, give them the AD drugs and put them into groups to organize results, to see variation in results and to track how effective these drugs are in the brain. After they take the drugs, they will take a CT scan, a PET scan, memory tests, cognitive tests and surveys. These tests will be our indicator if these drugs are effective. Our research question for this proposal is how effective are the AD drugs Aricept, Exelon, Ebixa and Lamivudine compared side by side, when it comes to slowing in the progression of the disease for the symptoms of memory loss and cognitive function loss in the brain?

Research Approach

A longitudinal study design will be used for this proposal because we are looking to see if the drugs are effective in patients that have AD. This requires us to look over the course of 6 months to 5 years. We are looking this long because we have a large population to study and AD can last for many years with the symptoms of memory loss and cognitive function loss. We are also looking this long because we want to know what changes occur in the brain as a result of taking these drugs for AD, meaning do these drugs work or not in slowing memory loss and cognitive function loss. This proposal will also be required to be a randomized control trial because participants will be followed over time to look for the see the effectiveness of the drugs for AD patients and also because the patients in the proposal will be randomly assigned to a group of 250 people to test the effectiveness of the drugs on the symptoms of cognitive function loss and memory loss. The population of 1,000 people is broken down into a group of 250 people, to see if there is any variation in results for each person taking the drugs. For this proposal, patients with AD, who are assigned to a group, will take the drugs. Then, over the course of 6 months to 5 years, researchers will observe to see, if there are any changes in the brain via PET scans and CT scans and see if the symptoms of memory loss and cognitive function loss were slowed in progression. Over the course of time while these patients take these drugs, effectiveness of the drugs will be tested via memory tests, cognition tests and surveys to see what has changed since taking the drugs.

Population & Sampling

This proposal's target population is patients with AD nationally who are between the age of 45 and 90 years old. This age range is chosen because this is the typical age range people could be diagnosed with AD. There is no difference with early onset AD that could be a confounding variable, when it comes to effectiveness of the treatment. Since this proposal involves a population that is geographically spread out, cluster sampling will be used to analyze these populations that are pre-defined. In this case, since the population is national, this proposal requires a large population of individuals to have a proper representation of people who have AD across these ages. This proposal requires a large population to see how each person responds to the drugs and to see variation in data results. For this proposal, 1,000 people nationwide would be needed to see if the drugs are effective in slowing the symptoms of memory loss and reduced cognitive function for AD. This study needs 1,000 people because every person will receive the four drugs and each drug will be taken individually spread out over the course of weeks to see the effects. When it comes to each group, each person will receive the four drugs to test effectiveness and to see if there is any variation in results. The data will be collected until the patients have completed the study for each drug or until the patient is unable to participate in the study anymore. Data for this study will be periodically collected to see the effectiveness of the drug over the course of months to years in the brain.

Operationalization & Measurement

Effectiveness of the drugs will be measured through memory tests, cognition tests and surveys, PET scans and CT scans. Effectiveness in this case is defined as treatment that works in slowing progression of the symptoms of cognitive function loss and memory loss in AD patients. This is will be done by seeing if the drugs work in these patients. PET scans and CT scans will be used to see what parts of the brain are affected as a result of taking the drugs. Positron Emission Tomography also known as PET scans are image tests used to help see how tissues and organs are functioning. Computerized Tomography also known as CT scans are a series of x-ray images used to see cross-sectional images of the brain, bones, soft-tissues, blood vessels and other parts of the body. This will allow researchers to see what parts of the brain are affected, as a result of the drugs and in-turn will explain what symptoms are seen and which ones are not for AD patients. It will also allow researchers to see the progression of the disease and its effect on slowing the symptoms of memory loss and cognitive function loss.

When it comes to this study, the independent variable for this will be the AD drugs themselves which are Aricept, Exelon, Ebixa, Lamivudine. Based on this each drug will be taken individually spread out over the course of weeks to see the effects of the drug on the brain. The dosage for Aricept is between 5 mg and 23 mg (FDA, 2012). The dosage for Exelon is between 6 mg and 12 mg (FDA, 2013). The dosage for Ebixa is between 5 mg and 20 mg (FDA, 2013). The dosage for each of the drugs mentioned earlier for this study will depend on the drug. Some of the drugs require a low dosage to be effective and some require a high dosage to be effective. Overall, the dosage will increase to see the effectiveness of the drugs and to see if dosage affects the effectiveness of the drugs for these patients with AD. Dosage will be monitored for each person because it's understood that not everyone can handle the recommended dosage for AD patients. Also, this is to ensure that the patients are safe when it comes to the drugs. The dependent variable for this study will be effectiveness of the AD drugs in slowing the progression of memory loss and cognitive function loss for AD, which will be done through cognitive tests, memory tests, surveys, PET scans, and CT scans.

Data Collection

For this study, data will be collected through memory tests, brain scans, surveys and cognition tests. The memory test will be done each time an AD patient takes the drugs to see if their memory has changed since taking the drug and to monitor the symptom of memory loss. The memory test will consist of researchers asking the patient if they remember a set of items presented or a set of answers to questions. This test will be visual and auditory. PET scans and CT scans are used to see if there are any changes in the brain, to monitor the progression of the disease and to see the effects of the drugs on the brain. This will be done throughout the course of the study with each drug. The surveys will be done to see if the patients have experienced any changes since taking the drugs. This test will consist of asking the patient their experience since taking the drug and any symptoms they have experienced since taking the drugs. The cognition test will be done to test intelligence and decision-making skills. This test will be visual, auditory and written. This test will involve the researchers asking simple mathematic and reading questions and providing a common-sense scenario to the patients. Data will be collected weekly. These tests are valid because other studies like (Valcour, 2011) have used these tests to see the effectiveness of a drug.

Analysis

The data in the study will be analyzed using a quantitative method. This method will be useful for this study because we are looking to see, which drugs are effective. This is done through the memory test and cognitive test data. If the patients score high on these tests after receiving the drug, then it will show they are effective. This would match with what is expected for the hypothesis. If they score low on these tests after receiving the drug, then it will show they are not effective. The PET and CT scan data will also be important, when it comes to

quantitative data because it will be looking at how many regions of the brain are affected by the drug, which will be important in determining if the brain is affected by the drug and if it slows the symptoms. In all multivariate statistical analysis will be used to compile all this data to see, which drugs are effective in slowing the progression of memory loss and cognitive function loss. This will be done by looking at multiple variables like scores on memory and cognitive tests to see, which drugs had the highest test score data.

Ethical Considerations

The ethical considerations to consider when it comes to this proposal are the side effects of these drugs. The drug Aricept has side effects like trouble with sleeping, nausea, vomiting and muscle cramps. The drug Exelon has side effects like diarrhea, dizziness, headaches and nausea. The drug Ebixa has side effects like dizziness, hypertension, headaches and somnolence. The drug Lamivudine has side effects like headaches, belching, heartburn and depression. The last ethical consideration for this study will be anonymity of the patients involved in this study. These ethical concerns can be addressed by not sharing the identity information of the patient, letting the patients know ahead of time the drug side effects through informed consent and not denying treatment to the patients who are in the study. Getting informed consent from the participant or a caretaker to participate in this study is important because we want that patients to be treated fairly. When it comes to this study, patients have the option to dropout and caretakers have the option to discontinue the study for the patient. If one drug is doing better than another one, then the study will not stop. Once all the drugs have been tested then the study will stop. The study will go through the IRB review for approval.

Discussion & Future Directions

Significance

Alzheimer's Disease is a disease that affects millions of people worldwide. Alzheimer's Disease still has no cure. This study is important because it could open doors into what AD drugs are effective and which ones still need more testing. This study is also important because researchers and scientists are looking at what drug treatments are effective in slowing the progression of the disease and its symptoms. This study is also important because it can open the doors for combination therapy and help lay the foundation for non-human studies that look at disease.

Limitations

When it comes to this study, one of the limitations is cost. As the study continues from months to years, it will be expensive to keep up. The way to overcome this limitation is through having sponsors to fund this research and having drug companies pay for expenses. Also, the drugs are expensive to keep providing to the patients over the course of the study. The second limitation of the study is that there will be possible loss to follow up because AD has no cure. AD has medicine to treat the symptoms, but no drug currently has been able to cure someone of AD completely meaning death is expected, when it comes to AD patients. One way to overcome this limitation is to segment the study into consecutive time segments. The third limitation for the study is that on one of the drugs they were not able to identify all the target areas in the brain when it comes to the drug and that some of the pathways may have been restricted. The last limitation of this study is taking these drugs over a long period of time, may affect the effectiveness of the drugs in AD patient. The patients will be monitored by doctors, when it comes to this.

Future Directions

This method of testing effectiveness could be used when testing other AD drugs. This research in the future could provide insight into why some drugs affect different parts of the brain. When it comes to this research, it could help scientists and researchers better understand why these particular drugs slow the progression of the disease and others don't. The proposal could be useful, when it comes to combination therapy because combination therapy is huge part of AD treatment and seeing, which

treatments are effective and work well together can be useful in treating symptoms. This proposal could provide some groundwork for non-human studies like (Zhang et. al, 2018), when it comes to starting phase 1 and phase 2 of FDA clinical testing, because the drug BPN14770 was proven, to be effective in treating humanized mice with AD as a laboratory study and may provide some promise in humans, if it passes phase 1 and phase 2 of FDA clinical testing.

References

Alzheimer's Association. (2019). Facts and Figures. Retrieved December 11, 2019, from https://www.alz.org/alzheimers-dementia/facts-figures.

Alzheimer Society Of Canada. (2008, April). Ebixa. Retrieved December 11, 2019, from https://alzheimer.ca/sites/default/files/files/national/drugs/drug_ebixa_2008_e.pdf.

Casey, D., Antimisiaris, D., & O'Brien, J. (2010). Drugs for Alzheimer's disease: Are they effective? *P & T : A Peer-reviewed Journal for Formulary Management*, 35(4), 208-11.

Chatterjee, P., Roy, D., & Rathi, N. (2018). Epigenetic Drug Repositioning for Alzheimer's Disease Based on Epigenetic Targets in Human Interactome. J*ournal of Alzheimer's Disease: JAD*, 61(1), 53-65.

FDA. (2012). Aricept (donepezil hydrochloride) Label. Retrieved December 12, 2019, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020690s035,021720s008,022568s005lbl.pdf.

FDA. (2013, October). Exelon (rivastigmine tartrate) oral solution. Retrieved December 12, 2019, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020823s032,021025s022lbl.pdf.

FDA. (2013, October). Namenda (memantine HCl). Retrieved December 12, 2019, from https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s008lbl.pdf.

Flavell, L. (2019). Exelon (Rivastigmine). Retrieved December 11, 2019, from https://alzheimersnewstoday.com/alzheimers-disease-treatment/approved-drugs/exelon-rivastigmine/.

Frolich, L., Monsch, A., Kressig, R., Downs, P., Caputo, A., & Strohmaier, C. (2012). Comparisons of patient characteristics in subpopulations of the OPtimising Transdermal Exelon In Mild-to-moderate Alzheimer's disease (OPTIMA) study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 8(4), P603.

Graber, M., Dachs, R., & Darby-Stewart, A. (2011, March 15). Donepezil to manage Alzheimer disease: New vs. standard dosing. *American Family Physician,* 83(6), 742-4.

Hippius, H., & Neundörfer, G. (2003, March). The discovery of Alzheimer's disease. Retrieved October 12, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181715/.

McMaster University. (2018, January 25). What is Alzheimer's Disease? Retrieved December 11, 2019, from https://wiki.mcmaster.ca/LIFESCI_4M03/group_4_presentation_3_-_alzheimer_s_disease.

Molino, Ivana, Colucci, Luisa, Fasanaro, Angiola M., Traini, Enea, & Amenta, Francesco. (2013). Efficacy of memantine, donepezil, or their association in moderate-severe Alzheimer's disease: A review of clinical trials. *The Scientific World Journal,* Vol.13.

Onor, M. L., Trevisiol, M., & Aguglia, E. (2007). Rivastigmine in the treatment of Alzheimer's disease: an update. Retrieved December 12, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2684084/.

Rountree, S., Atri, A., Lopez, O., & Doody, R. (2013). Effectiveness of antidementia drugs in delaying Alzheimer's disease progression. Alzheimer's & Dementia: *The Journal of the Alzheimer's Association,* 9(3), 338-345.

Valcour, V. G. (2011, December). Evaluating cognitive impairment in the clinical setting: practical screening and assessment tools. Retrieved December 12, 2019, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6148899/.

WebMD. (2019). Aricept Oral : Uses, Side Effects, Interactions, Pictures, Warnings & Dosing. Retrieved December 11, 2019, from https://www.webmd.com/drugs/2/drug-14335/aricept-oral/details.

Zhang, C., Xu, Y., Chowdhary, A., Fox, D., Gurney, M. E., Zhang, H.-T., … O'Donnell, J. M. (2018, August 14). Memory enhancing effects of BPN14770, an allosteric inhibitor of phosphodiesterase-4D, in wild-type and humanized mice. Retrieved October 12, 2019, from https://www.nature.com/articles/s41386-018-0178-6.