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Emerging Treatments in Alzheimer's Disease

Abigail Harrelson
Grand Valley State University

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INTRODUCTION

Alzheimer's disease is a neurodegenerative disease common in the elderly. Some of the symptoms associated with the disease are deterioration of cognitive functions and loss of memory (3). These result in lowered ability to perform daily functions. For late-stage patients increased symptoms of dementia (7), including confusion, personality and speech changes, and eventually an almost vegetative state (9). While there are currently 4 million people that have the disease in the United States, it is estimated that by 2050 there will be over 16 million people living with Alzheimer's (9). One reason for this large increase in incidence and prevalence of Alzheimer's is the increase in life span, which has occurred due to the improved medical care over the last century (21). AD is already the third most costly medical condition in the US (22), and this combined with the large number of people that will be reaching the elderly stage (over 65) in the next few decades, it is important to find an efficient treatment for this disease, since the current therapies do little to help. This review will look at emerging treatments in AD. First, it will give background on the disease, its pathology and current treatments. Newer therapies that may open up new treatment pathways will then be the focus.

BACKGROUND

There are several factors that have shown predisposition to this disease. There are several genetic factors, one that includes possession of a copy of the epsilon 4 variant of the apolipoprotein E gene (APOE4), which increases risk by a factor of 3 (having two copies of the gene increases risk by a factor of 10) (2). Another set of genetic variations, one on

the portion of chromosome 21 that codes for the amlyoid precursor protein (APP), and another on chromosome 14 in the presenilin-1 and -2 genes, both can result in Familial Alzheimer's Disease (FAD). These genetic mutations result in FAD, which accounts for 30-50 % of autosomal dominant, early onset cases (most with FAD present with symptoms between 40 and 65) (5). However, exposure to metals, smoking, high levels of cholesterol, and diabetes has also been shown to be factors in increased risk (8). We currently do not know if these cause AD or only correlate with the disease. Age is also one of the leading risk factors in the development of AD.

When a patient presents with Alzheimer's, several steps are involved in providing a positive diagnosis. First, a detailed history is compiled, followed by a standardized assessment of cognition and functional status and laboratory testing. For brain images, the majority of people undergo a magnetic resonance imaging (MRI) process to exclude other conditions and measure brain atrophy. Other doctors will choose to use biomarkers to determine if a patient is presenting with AD. Specifically, doctors would be looking for a quantification of amyloid-β species and tau species in certain body fluids, because these proteins are so closely linked to the pathology of Alzheimer's. In its prodromal stage, cerebrospinal fluid, obtained by lumbar puncture, appears to contain the most reliable biomarkers for testing for Alzheimer's. At later stages in the disease, cerebrospinal fluid, plasma, and urine can all be used to identify biomarkers (22). These steps are important in determining whether or not a person has Alzheimer's, yet unfortunately it can be expensive for someone to pay for these tests, mainly the MRI, especially if they do not have medical insurance (16).

Recently, a gene-based blood test was found to identify prodromal Alzheimer's with an accuracy of 81%. These results are based on three 2-year studies on more than 200 subjects. The blood test uses 25 genes that are known to be active in the biological processes associated with AD, including oxidative stress, neuronal function, and regulating the processing of amyloid and tau. It is believed that this test will be ready to be submitted to the US Food and Drug Administration within the next year. If this blood test is approved, it would most likely be conducted at a primary-care physicians office, with results back in a few days. This test should provide an effective way of diagnosing AD without doing an invasive procedure to look at biomarkers (26).

There are several pathological pathways that are associated with AD. The first is accumulation of proteins, namely neurofibrillary tangles and β-amyloid. The accumulation of these tangles is caused by hyperphosphorylation of cytoskeletal tau protein, along with deposition of amyloid-β protein as senile plaques (3). In AD, glycosylation is reduced in brain tissue, which appears to alter neuronal function, most likely through the hyperphosphorylation of specific tau proteins. Hyperphosphorylation of tau seems to cause tau to aggregate, which results in the neurofibrillary tangles that are characteristic of Alzheimer's (17). A second pathway that could to AD is severe neuronal death. This is caused by glutamatergic excitotoxicity (excessive stimulation). The neuronal death takes place by one of two mechanisms. One pathway causes delayed neuronal apoptosis when there is moderately excessive intraneuronal calcium influx, coupled with oxidative stress. The other pathway causes immediate neuronal death when there is severely excessive intraneuronal calcium influx (12). Both of these mechanisms of neuronal death result in the loss of memory and learning, which are key symptoms of

AD. A final pathological process that is associated with AD is the production of reactive astrocytes in the entorhinal cortex, hippocampus, amygdala, and areas of the temporal, parietal, occipital, and frontal cortex (13).

Evidence has shown that one of the first places to be affected in the course of the disease is the hippocampus, which is important in both memory and learning. The hippocampus lies under the medial temporal lobe of the brain, one on each side. Based on this, a potential therapy has evolved, involving preserving the production of new neurons in the hippocampus. Several molecules that are key to AD pathogenesis are also important in regulating neurogenesis in the hippocampus, so it has been thought that if this neurogenesis can be increased, it might be an effective treatment against the disease. One way this therapy was tested was by looking at physical exercise and/or exposure to an enriched environment (EE), a positive regulator of neurogenesis. This showed an increase in cognitive performance in transgenic mouse models of AD. However, in transgenic mice with different models of AD (FAD-linked PS1 variants or forebrain-specific PS1 knockout mice) an enriched enviroment does not enhance neurogenesis. Even further, EE in APOE4 transgenic mice actually suppresses neurogenesis. This indicates that the impact of physical exercise and EE on neurogenesis vary among different types of mouse models of AD. More experiments need to be done investigating the impact of exercise and EE on mice with different aspects of AD pathology in order to truly determine the effectiveness of this therapy (3).

At this point, there are three main mechanisms that have been shown to explain the causes of Alzheimer's disease. In the first, amyloid plaques, because of extracellular aggregation of Aβ42 peptide, create inflammation and oxidant stress. The second

mechanism describes neurofibrillary degeneration from an increase in phosphorylation of tau protein aggregating in neurofibrillary tangles. The final mechanism involves glutamatergic neuronal excitotoxicity due to the localization of amyloid beta peptides and phosphorylated tau, which leads to increased calcium entering the postsynaptic neuron. This ends in neuronal necrosis and apoptosis. The problem with developing a treatment for AD is that it might combat one of the mechanisms, but not necessarily the other two. Also, testing new drugs is challenging, because most require patients with no neurodegenerative lesions at the very earliest stages of AD. Because of the difficulty in recognizing Alzheimer's at this stage, there is a very limited selection of patients (14).

This early stage, called prodromal Alzheimer's, was first recognized as a concept in 2000 to refine the concept of mild cognitive impairment. Mild cognitive impairment (MCI) was broken up into three categories to make treatment easier, one being 'MCI of Alzheimer type' (aka: prodromal Alzheimer's). By associating a form of MCI with Alzheimer's, it allows for the possibility of preventing full-onset AD prior to the onset of symptoms. Diagnostic criteria for prodromal AD include memory complaints, progressive onset, mildly impaired complex activities of daily living, persistence of memory changes after assessment, absence of the fully developed dementia, and exclusion of other disorders that could cause MCI (through test, neuroimaging, and biomarkers). One of the primary criteria for differentiating prodromal AD from other forms of MCI is amnestic syndrome of the hippocampal type (one of the main areas of the brain impacted by AD). These include the inability to free recall information, despite adequate cueing, and decreased total recall due to impaired recognition (27).

CURRENT DRUGS

Since AD patients present with loss of cortical neurons and cholinergic function, the initial targets for treatment were cholinesterase inhibitors (ChEIs). ChEIs are one of two current FDA approved drugs for AD, and are used in mild to moderate cases. The most common ChEI prescribed is donepezil, which works to protect the cholinergic neurons from degeneration. Memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist, is the other drug, and is used in moderate to severe cases. This drug was developed because increased activation of NMDA receptors is thought to lead to neuronal death. Both classes of drugs are shown to have side effects, with memantine most frequently reporting dizziness, headache, and constipation (25), and donepezil reporting nausea/vomiting, insomnia, and diarrhea. In combination with these side effects is the fact that both drugs only provide symptomatic relief, and do nothing to alter disease progression. This lack of treatment is the reason that so many new treatment methods are currently being worked on, with three different treatment goals being looked at: preventative, disease-modifying, and symptomatic (9).

NEW TARGETS

Competitive Inhibitors

One focal point for new therapies is a membrane imbedded protease γ-secretase, which is an enzyme involved in the increased production of the amyloid-β peptides. The only γ-secretase substrate that has been linked to Alzheimer's is C99, which is a 99-amino acid long C-terminal domain of Amyloid Precursor Protein (APP). This C99 substrate has been shown to contain 25 amino acids of which mutation could result in FAD mutations. When tested, it has been shown that FAD mutations mainly affect the enzyme's interaction with the C99 substrate, yet the active site remains intact. There is a sequence

along the C99 substrate, the Aβ sequence, which is attributed to AD when there is an increase in the Aβ42/Aβ40 ratio. The lowest ratio is produced when Aβ40 is the dominant product of the Aβ sequence, which is the normal result. When there is either a gain in production of Aβ42 or a loss in production of Aβ40, then the risk of AD increases. A 30% decrease in Aβ40 production was observed in studies of the disease pathogenesis, while those with no change in Aβ40 production did not present with the disease. These results indicate that control of the Aβ sequence could be beneficial in decreasing risk of Alzheimer's.

Multiple studies have been conducted on humans, experimental animals, and cells that show that in all cases of gradual saturation of γ-secretase, molecular events have occurred that are associated with the pathogenesis of the disease. Based on these findings, a therapy needs to be designed that decreases the amount of enzyme saturation with its C99 substrate. The ideal therapy would increase the Km (the Michaelis-Menton constant, a concentration value) for C99 substrate, but would be a standard competitive inhibitor of Aβ 1-40 and would have little to no effect on the Aβ42/Aβ40 ratio. These therapies need to be competitive inhibitors, because noncompetitive inhibitors, such as DAPT (*N*-[*N*-(3,5-difluorophenacetyl)-L-alanyl]-*S*-phenylglycine *t*-butyl ester), cause a decrease in enzyme catalytic capacity, making the enzyme saturated even at lower than normal levels of C99 substrate, which is contradictory to what is desired. Further studies have shown that different genetic mutations have shown an increase in the Aβ42/Aβ40 ratio when the catalytic capacity of γ-secretase is decreased. A therapy has to combine decreased saturation of the C99 substrate with a competitive inhibitor that will not cause the enzyme to become prematurely saturated (4).

Selective Inhibitors

Several drugs have been developed with an impact on the cholingeric system that are mainly selective inhibitors of acteylcholinesterase (AChE). Compounds inhibiting AChE can bind at three places; if they bind at the active site they will interact with esteratic or the anionic site. They could also interact with the aromatic gorge or the periperal (β) anionic site. Inhibitors of the esteratic subunit of the active site are usually nerve agents, many toxins or pesticides. One of these inhibitors is rivastigmine, a symptomatic drug treatment for AD and Parkinson's. While inhibitors at the esteratic site are non-reversible, compounds that interact with the anionic site are reversible. Tacrine (9-amino-1,2,3,4,-tetrahydroacridine, marketed under the name Cognex) is one such anionic site inhibitor. Tacrine would be promising treatment for AD, unfortunately it has high hepatotoxicity, so until a less toxic derivative of tacrine is found, it must be used selectively. Galantamine, an alkaloid from the Caucasian snowdrop (*Galanthus woronowii*), marketed under the name Nivalin, is an anionic site inhibitor, as well as an aromatic gorge inhibitor. While all these are promising, the main targets of AD treatment are inhibitors of the peripheral anionic site, because they are considered not only symptomatic but also possibly causative ones. Examples of drugs of this type are man-made donepezil, trade name Aricept, and huperzine, which come from the firmoss *Huperzia serrata*. Drugs that bind at the peripheral and anionic site cause elevated levels of AChE, while drugs that bind at the esteratic site do not change AChE levels. Unfortunately, the increase in AChE is a downside to the treatment efficacy, but other than this AChE increase peripheral anionic site drugs are proving to be a promising causative treatment for AD (20).

Enzyme Therapy

With the assumption of Aβ plaque buildup being a main cause of Alzheimer's, several enzymes have been targeted as possible treatments. The first target is β-secretase, which cleaves APP, and the amount of Aβ generated is regulated by the extent of APP cleavage. Therefore, it has been thought that if you can inhibit the β-secretase, the Aβ plaques will not be formed.

The other treatment target is γ-secretase. This enzyme contains several integral membrane proteins. The most common substrate of γ-secretase is APP, which produces Aβ40 and Aβ42 peptides. Based on this, if the production of γ-secretase were halted, then the production of Aβ would also decrease, reducing the plaque buildup, and possibly stopping neurodegeneration. In addition, the major subunit of γ-secretase is PS1/PS2, which has multiple mutations that cause FAD. Studies were conducted that showed that reducing PS1 levels increased the amount of Aβ42, but did not affect Aβ40. In contrast, when γ-secretase was increased by expressing all four of its subunits, the Aβ42/Aβ40 ratio was reduced. A reduction in this ratio is an effect that is contrary to that shown with FAD mutation of PS1. These studies show that FAD mutations lead to loss of function, and that loss of function seems to affect γ-secretase processing rather than PS1 or PS2 functioning. Based on these results, γ-secretase has been tested to see whether it would really treat AD if γ-secretase were inhibited. Unfortunately, a loss of γ-secretase function showed an increase in cancer, as well as an increase in a severe form of acne inversa; therefore it would not make a good treatment. Further research must be done to determine whether inhibition of β-secretase would cause any adverse affects (8).

Antioxidants

One preventative approach being studied is antioxidant therapy. It has been shown that early in the disease, reactive oxygen species (ROS, produced in the mitochondria) damage is present (from leakage from the mitochondria), so it would make sense to treat with antioxidant therapy. A plus of this treatment would be that antioxidants are available through dietary means, making it easy and cheaper than most drugs. Several studies found folate supplementation to show a reduced risk of Alzheimer's. In addition, therapy with both vitamins E and C has shown reduced incidence of AD, and vitamin E may actually slow the progression. While dietary antioxidants are used, so are pharmaceutical antioxidants, namely mitochondrial antioxidants. One therapy tested, Coenzyme Q_{10} (CoQ_{10}) shows neuroprotective effects, including inhibition of toxic free radical production and reduced ROS injury. Unfortunately, this treatment only works with fully intact and functioning electron transport chains (ETC), because CoQ_{10} is responsible for carrying high-energy electrons through oxidation and reduction in the ETC. Since damaged mitochondria, and consequently damaged ETCs, are common in early AD, this treatment is not practical for anyone already showing symptoms of AD. While CoQ_{10} does not seem feasible as a treatment method, a similar compound, MitoQ, is shown to have the same effects as CoQ_{10} (reduced ROS injury), it does not require a fully intact ETC to work properly, since it is not as involved in the chain as CoQ_{10} is (9).

Hormones

Hormone levels are promising in as a disease modification therapy. Altered hormone levels appears to play a role in AD, which is shown in the increased incidence of AD in women, since they experience hormone changes when going through menopause. The

most drastic hormone change during this time is luteinizing hormone (LH), which doubles in production. The significance of this hormone change is further exasperated by the fact that men with Down's syndrome, who have elevated LH levels, are more likely to develop AD than women with Down's. This trend, similar to women who have experienced menopause, shows a direct link between AD and LH level. Overall, patients with AD show LH concentrations twice as high as non-AD patients the same age. A new drug, leuprolide acetate, has been shown to reduce these LH levels, and in Phase II clinical trials decreased cognitive decline and stabilized activities of daily living in patients with mild to moderate Alzheimer's. Based on these findings, therapies to decrease LH look to be a very promising treatment (9).

The major secretion from the adrenal gland, dehydroepiandrosterone (DHEA), has been shown to slow delay brain aging by recovering the impairment of growth factors. A decrease in DHEA production is the most common age-related change in the adrenal cortex. DHEA also has antioxidant, anti-inflammatory, and ultimately anti-aging affects. While DHEA has been proven to be effective therapy in non-elderly patients with cognitive decline, it has yet to be tested in patients with advanced age. Therefore, a study was conducted testing the ability of DHEA as a treatment in experimental AD rodents by measuring oxidative stress biomarkers, antioxidant status, neurotropic factor BDNF, and cholinergic markers. The data from the study concluded that DHEA produced significant increase in oxidative stress markers, activation of the antioxidant enzymes, and enhancement of BDNF and acetylcholine levels. Based on these results, it can be concluded that DHEA has an important role in characterizing AD through its antioxidant, neurotrophic properties, and cholinesterase-inhibiting activity. Since this experiment was

completed on rats, the next step is putting together a clinical trial in order to see if these same properties apply in a human model (13).

Sex Hormones

Sex hormones have also shown to have protective actions against Alzheimer's. While sex hormones are currently recognized for their neuroprotective properties, translating these into an efficient treatment or prevention strategy for AD has been largely unrecognized, even though evidence suggests that neural actions estrogens, androgens, and possibly progestogens can reduce the risk of AD (23).

The most important of these sex hormones might be estrogen, which was brought to the attention of researchers due to the higher prevalence and incidence of AD in females. There is a stronger association between the apolipoprotein E allele in women than men, as well as a greater severity of AD in women indicated by differences in neuropathy and cognitive deficits between sexes. These both indicate that women might be at a higher risk for AD, even when their longer lifespan is taken into account. Several studies were done in transgenic mouse models that exhibit sex differences in AD-like neuropathy similar to humans, mostly through a greater Aβ deposition that was observed in female mice, which suggest the female brain might be more vulnerable (23).

This increased risk is presumed to be associated with the loss of estrogens and progesterone that women suffer at menopause. Further, compared to women of the same age without AD, women with AD have even lower levels of estrogen. Estrogen has the ability to protect against neuronal loss induced by the neurodegenerative agent Aβ, and several reports show estrogen to protect neurons and neural cell lines from Aβ mediated toxicity and could promote Aβ. Estrogen might also regulate APP processing through

protein kinase C (PKC) dependent pathways. Also, estrogen and progesterone both have the ability to regulate levels of tau phosphorylation (23).

Estrogen has been studied alone, as well as estrogen combined with progesterone. However, multiple reports show that progesterone often antagonizes the estrogen-mediated neuroprotective actions, rather than synergizing with the estrogen. One drug, tamoxifen, an antiestrogen most commonly used to treat breast cancer. It has been found that low concentrations of tamoxifen can protect cultured neurons from toxicity due to Aβ. This suggests the possibility of tamoxifen's use as a potential treatment against AD. Because this is a new finding, the potential benefits of tamoxifen in postmenopausal women for prevention and/or treatment of Alzheimer's has not been well studied, but should be seriously considered for research based on the information presented (23).

Antidepressants

A symptomatic approach being tested involves antidepressants. About 35% of Alzheimer's patients develop depression at some point during the disease. Patients with AD have an insufficient amount of the neurotransmitters dopamine, norepinephrine, and serotonin, because of cortical atrophy. Selective serotonin reuptake inhibitors (SSRIs) have been shown to improve depression and enhance quality of life. In addition, antidepressant therapy is the only therapeutic intervention that has shown significant improvement in patients with mild impairment. All of these treatments have shown to improve the quality of life for AD patients, and some have shown to slow disease progression, but in the future it is important to keep testing them in trials, and to combine them with other therapies to get the maximum therapeutic benefit for the patient (9).

Combined Therapies

Donepezil is now being paired with other drugs in order to maximize treatment, since it is one of the few drugs that have shown any positive improvements. Studies have been done that indicate that improving blood supply to the brain might help in the treatment and/or rehabilitation in AD patients, so donepezil has been paired with natural hirudin, a direct thrombin inhibitor, which varies from normal anti-coagulants in that does not have the potential to cause bleeding or inhibit blood-clotting. To test this, a study was done using 84 patients testing treatment with donepezil alone and donepezil combined with hirudin. At the beginning of the trial, each patient received an Alzheimer's Disease Assessment Scale cognitive (ADAS-Cog) score ranging from 0-70, with the higher score indicating more cognitive impairment. In the patients treated with the combined treatment had a significant decrease in ADAS-Cog scores. When you compare this result to the donepezil group alone, the scores in the combined treatment group were lowered by a significantly larger amount than in donepezil alone. Cognition was also improved in the combined group over an 8-week period. While there was a statistical significance between the two groups, a larger study would be conducted in order to get a further understanding of the effectiveness of the combined therapy, as well as a study that takes place over a longer period of time, to determine the lasting effects of the results (the current study lasted only 20 weeks) (7).

Memantine, the NMDA discussed earlier that is approved by the FDA, has no immediate treatment effect. However, after 3 to 6 months of use, patients have reported better cognitive performance. This makes sense, because memantine is used to treat symptoms and help to slow disease progression, but does not stop it completely. When treating with memantine, neuronal death still occurs, so it was hypothesized that coupling

memantine with an antioxidant would be better at protecting against neuronal death and declines in cognitive performance. The antioxidant chosen to test this was vitamin D, which is hormone that crosses the blood-brain barrier and binds to receptors in the central nervous system. Not only has vitamin D been known to help cognitive decline, but it also has been shown to improve gait performance, another complication of AD. The pathways of hypovitaminosis D and cognitive decline in Alzheimer's are smiliar, with both based on the calcium neurotoxicity and the changes in protective mechanisms against glutamatergic excitotoxicity. It is for this reason that vitamin D was chosen as a couple to memantine for a study in combination treatment. For the results, a decrease on the ADAS-Cog score of at least 3 points will be considered relevant. This trial is currently being recruited for completion, yet based on the initial findings and the positive aspects of each on their own, the findings from the trial are expected to be positive for coupling memantine with vitamin D in treating cognitive decline in Alzheimer's patients (12).

A study was conducted that involved determining the effects of continued donepezil treatment on patients living in community-living residencies, and whether or not adding memantine to this treatment was beneficial. The study had three objectives. The first, to test whether over a 1-year period continued or discontinued donepezil treatment was more effective in improving cognition. The second objective was whether or not the addition of memantine was helpful, and the third, to test if the combined treatment would have additive or syngeristic benefits. After the one-year test period, the following results were found. Continuing donepezil showed significant improvement on the Standardized Mini-Mental State Examination (SMMSE), and while memantine therapy allowed showed an improvement in SMMSE scores, it was not as large as the

donepezil therapy. In regards to the third objective, it was found that combined treatment with both donepezil and memantine was not significantly better than treatment with donepezil alone. These results show that the first two objectives had statistically significant positive results, while the third objective did not (15).

Immunotherapy

Amyloid-β (Aβ) immunotherapy is an emerging approach to combat AD, yet it appears to be most effective in treating the disease in its later stages. In searching for a therapy to combat early disease pathology, it was hypothesized that anti-inflammatory cytokine signaling, specifically interleukin-4 (IL-4), efficiently enhances Aβ clearance, synaptic transmission, and amelioration of AD progression. This was tested on mice, and the results showed that IL-4 enhances neurogenesis in mouse neural progenitor cells cocultured with IL-4 stimulated microglia in the presence of Aβ peptide. This study was the first that showed that central nervous system expression of IL-4 could directly stimulate neurogenesis. This suggests that IL-4 is likely to enhance neuronal progenitor cell proliferation, and neuronal differentiation. It was shown that neuronal expression of the anti-inflammatory interleukin-4 restores the spatial learning function of mice through its effect on Aβ reduction, glial activation, and neurogenesis. The study also showed that IL-4 could function as neuromodulators or neurohormones. These results all show that it should be possible to treat neurodegenerative disorders through anti-inflammatory signaling cascades in the brain (19).

Antiviral Agents

There is increasing evidence that herpes simplex virus 1 (HSV1), a neurotropic virus infecting most humans and causes herpes simplex encephalitis (HSE), has a role in

Alzheimer's. This connection was first established because in those affected with HSE, the same areas of the brain are impacted as those in AD. Since the virus is also present in many older adults, and those with the apolipoprotein E gene, which has been linked to AD, it was suggested that HSV1 is connected to Alzheimer's. Because of this, it has been hypothesized that an antiviral agent would be beneficial in treating AD. Most antiviral agents currently target viral DNA replication. Therefore, it had to be determined if the accumulation of Aβ and tau protein, important steps in the formation of the disease, occurred through the process of viral DNA replication or independently of the replication process. A study was done to determine which pathway this accumulation followed. It was determined that tau protein formation is dependent on viral DNA replication directly (or on a protein dependent on it). Three antiviral agents were tested, acyclovir, penciclovir, and foscarnet, and all three inhibited tau formation. Conversely, when Aβ accumulation was tested, it was not completely inhibited by the antivirals, although it was partially inhibited (accumulation of about 20-30% of the normal amount was left, when the antivirals were used in high doses). The results of this study show that an antiviral agent would not only stop HSV1 replication, it would also provide effective treatment for Alzheimer's disease (11).

Allopregnanolone

It has been previously demonstrated that allopregnanolone (APα) increased proliferation of neural progenitor cells *in vitro*. The optimal treatment regimen of APα was found to be APα administered once a week for 6 months for promotion of neurogenesis and reduction of AD effects. During the study that determined this optimal treatment, it was indicated that APα is most effective in the pre-pathology, or very early stages, of the

disease. The appearance of the amyloid-β plaques coincides with the end of APα efficacy. The deposition of Aβ in the extracellular components of the cell leads to this loss of efficiency. This data indicates that the key point in regulating therapeutic efficacy is the presence of intraneuronal Aβ plaques. Overall, APα would be most beneficial when brains still have neurogenic and myelination capacity, meaning this treatment could only be used in patients with very early stage AD, or in those diagnosed with general mild cognitive impairment (10).

Sleep Therapy

Many patients suffering from AD are subject to sleep disturbances, which can lead to increased risk for physiological and physical problems. Sleep problems are one of the leading factors in patient institutionalization, because it affects both patient and caregiver. Sleep disturbances can be hard to treat, because sedatives can have many side effects. Because of this, two alternate therapies were suggested, increased daytime activity and bright light therapy, or a combination of the two. During a two month active treatment period, patients were awake for an average of 37 minutes per night less than the control subjects, and were overall asleep a greater portion of their time spent in bed, for all treatment methods (daytime activity, light therapy, or a combination). Unfortunately, sleep improvements were not sustained at the six-month posttest point. Based on these results, it can be deduced that if this treatment were continued with caregiver assistance, it would improve sleep the longer that the therapy was in use (1).

Treatment Facility

Many people wonder whether they should be treated at memory clinics for their AD, or whether their general practitioner would be sufficient in treating the disease, so a study

was conducted to determine the effectiveness of the two types of post-diagnosis treatment. Participants were assigned to one or the other, and then treated for a period of a year. Results were based on patients scores based on different scales. After the study, no evidence was found showing a difference in effectiveness between the memory clinics and general practitioners based on treatment and coordination of care. The only difference shown between the two was that the general practitioner group had a small positive effect on anxiety and the mood of the caregivers, although this result was not statistically significant (6).

Reduction of Aβ:

End-stage Alzheimer's has been shown to trace back to one simple process, the ordered aggregation of amyloid- β in the brain. While researchers cannot agree on how Aβ aggregation actually distrupts the brains function, it has been shown that reducing the amount of Aβ present will be sufficient to provide a therapeutic treatment. There are three ways this therapy could be achieved. First would be to inhibit the enzymes that cause Aβ to release from its parent protein. A second therapy would be to promote cellular Aβ degradation, and third, to stimulate immune-mediated removal of Aβ. All of these treatment options should provide a therapy for AD, although a combination might be required in order to provide full efficacy (24).

SUMMARY

Several new therapies have been studied in regards to the treatment of Alzheimer's disease, many with promising outlooks. This review has given a background of the disease along with the current available treatments, and then indicated emerging treatments that are being focused on. Several of these emerging treatments have been

shown to improve the quality of life in patients, and a few have also proven to slow disease progression. Therefore, future research should focus on the treatments described above and the testing of them in clinical trials, especially in the area of combined therapy, which researchers believe will provide the maximum benefit to the patient. There has been strong evidence that the disease pathology starts much earlier than symptoms show (18). So, while it is hard to find patients that fit the criteria of AD, trials should focus on patients at the earliest stages of the disease, because if an effective treatment can be found at that stage, treatments for moderate to late stage AD will not be necessary (not to mention patients and their families will not have to suffer through late stage AD). All of the treatments discussed above are promising, and hopefully through further research one, or more likely a combination, will provide the key to stopping Alzheimer's disease progression.

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