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# TREATMENT COMBINATION FOR ALZHEIMER DISEASE: CURRENT AND FUTURE PHARMACOTHERAPY OPTIONS

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## ABSTRACT

*There are several stages of Alzheimer's disease, ranging from early memory loss to functional reliance and death. We go over the assessment and diagnosis of mild cognitive impairment using a case study, as well as the diagnosis and treatment of Alzheimer's disease at every stage, including the treatment of the disease's cognitive and behavioral/psychiatric components as well as end-stage and end-of-life care.One Seventy percent of dementia cases are caused by Alzheimer's disease (AD), which is the sixth most common cause of death. By 2050, there will likely be 106.8 million instances of AD worldwide, up from 26.6 million in 2006. In 2010, the estimated global expenses of dementia were US$604 billion, or 1% of global GDP from windows in the economy. The overview of AD pathophysiology and treatment is the main emphasis of this paper.*

*The literature search was conducted using PubMed, ScienceDirect, Scopus, and Google Scholar as sources.*

*AD is typically thought of as a disorder that involves a more severe loss of neurons and synapses that occurs in different anatomic al locations and produces a variety of symptoms.*

*Numerous mechanisms, including cholinergic dysfunction, amyloid/tau toxicity, and oxidative stress/mitochondrial dysfunction, are attributed to the etiology of Alzheimer's disease.Herbal medications, secondary metabolites, and, to a lesser degree, non-pharmacological therapies are emerging and promising options for the treatment of AD in addition to the numerous therapeutic ta rgets, biomarkers, and pharmacotherapies currently available.*

*The precise mechanism of herbal medications, secondary metabolites, and non-pharmacological therapy for the treatent of AD needs to be further investigated.*

**KEYWORDS:** *Dementia, Differential Diagnosis, End Of Life, Mil, Alzheimer's Disease, Mitochondrial Dysfunction, Biomarkers Herbal Drugs*

## INTRODUCTION

Alzheimer's disease is a brain ailment that gradually impairs thinking and memory, and ultimately the capacity to do anything at all. a degenerative illness that impairs memory and other critical mental processes. Memory and other mental processes are eventually destroyed as brain cell connections and the cells themselves deteriorate and die. Wide swaths of the cerebral cortex and hippocampus are impacted by Alzheimer's disease, a neurodegenerative condition that progresses and never stops. The brain tissue including the frontal and temporal lobes is typically where abnormalities are initially identified. They then gradually spread to other parts of the neocortex at rates that differ greatly from person to person. The primary cause of dementia is Alzheimer's disease (AD), one of the biggest health care issues of our century. According to estimates, 40 million individuals worldwide suffer from dementia, and this figure is expected to double every 20 years until around 2050.The majority of dementia patients are over 60, and as lifespans continue to increase, the number of dementia patients—primarily AD patients—is rapidly rising. As a result, research on dementia treatment is rapidly expanding. Nevertheless, there are currently no effective therapy options for the disease, despite all of the diligent research efforts.

Although the illness lasts for 8 to 10 years on average, preclinical and prodromal stages usually last for more than 20 years before the clinical symptomatic phases. The most prevalent kind of Alzheimer's disease, sporadic, often manifests about age 80. The inability to remove Aβ peptide from brain tissue is the primary reason. However, at this age, co-morbid conditions including hippocampus sclerosis and cerebrovascular disease are common, making diagnosis and treatment more difficult. While sporadic disease frequently has a family history of afflicted near relatives, autosomal dominant inherited Alzheimer's disease affects only a small percentage of people (<1%). The primary cause of dementia and one of the biggest medical care challenges of our century is Alzheimer's disease (AD). According to estimates, 40 million individuals worldwide suffer from dementia, and this figure is expected to double every 20 years until around 2050.The majority of dementia patients are over 60, and as lifespans continue to

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increase, the number of dementia patients—primarily AD patients—is rapidly rising. As a result, research on dementia treatment is rapidly expanding. Aggregation of the microtubule protein tau in neurofibrillary cells and the buildup of insoluble forms of amyloid-β (Aβ) in plaques in extracellular spaces and blood vessel walls are linked to Alzheimer's disease. A complex family of enzymes cleaves the amyloid precursor protein (APP) proteolytically to produce Aβ.6.

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However, at this age, co-morbid conditions including hippocampus sclerosis and cerebrovascular disease are common, making diagnosis and treatment more difficult. While sporadic disease frequently has a family history of afflicted near relatives, autosomal dominant inherited Alzheimer's disease affects only a small percentage of people (<1%). The clinical syndrome known as dementia is defined by a progressive loss of ability to execute instrumental and/or basic activities of daily life in two or more cognitive domains, such as memory, language, executive and visuospatial function, personality, and behavior. Approximately 80% of dementia diagnoses are due to Alzheimer's disease (AD), which is by far the most prevalent cause of dementia.

Numerous microorganisms, including bacteria, fungi, and viruses, live in the gastrointestinal (GI) tract. These organisms are generally referred to as the gut microbiota (sometimes used interchangeably with "microbiome," which refers to the collection of genomes from all microorganisms). Through a variety of pathways controlling peripheral neurotransmitters, metabolites, and immunological signals, dysbiosis—an unbalanced community of gut microbiota—has been connected to a number of brain disorders, according to recently mounting data.

Molecules. Significant study in the subject was sparked less than ten years ago by studies that revealed changed gut microbiota composition in animal models and AD patients. Numerous investigations have since been carried out to determine the relationship between the gut microbiota and AD, and a number of mechanistic theories have been put forth to explain the role of microbiota in AD. These theories include the production of neuroactive compounds, immune system and metabolism modulation, blood-brain barrier regulation, and involvement in the formation and removal of Aβ plaques. Although this development raises the possibility that addressing the gut microbiota could be a therapeutic approach for AD, the topic of the "microbiota-gut-AD brain axis" is still in its infancy, and there are still a number of unanswered questions that must be resolved before Understand the intricate relationship between AD and the gut flora before implementing clinical treatments that aim to address it.

**THE MICROBIOTA-GUT-AD BRAIN AXIS IN OVERVIEW**

The notion that the gut and the brain are connected has been acknowledged for centuries in medical history, but in recent decades, the precise function of the microbiota in this gut-brain axis has come to light and is now a hot topic in both scientific research and public interest. The development of bioinformatics and high-throughput sequencing technology has allowed researchers to fully characterize the composition and function of the gut microbiota5, which has led to the field's exponential growth. Additionally, this technological development has created new opportunities to investigate the connection between neurological disorders like AD and the gut microbiome.

French neurologists Pinel and Esquirol were instrumental in the 19th-century medical adoption of the word dementia. The last third of that century saw the development of novel brain fixation and histological staining techniques, inhibitor therapy, and the identification of brain changes in a number of mental diseases (including syphilitic general paresis). Age-related sleep and wakefulness issues could be caused by a lowering of circadian rhythm amplitudes. Sleep and cognitive functioning in older adults and Alzheimer's patients seem to be improved by non-pharmacologically modifying circadian rhythms through a variety.

The disorder can be treated with a variety of medications, inc luding as N-methyl D

aspartate receptor antagonists (memantine) and acetylcholine sterase inhibitors (rivastigmine, galantamine, donepezil).

Alzheimer's disease has historically been regarded as an illne ss in which a progressive loss of neurons and synapses occur s in specific anatomical locations, leading to a variety of sym ptoms.

The location, distribution, and number of distinctive brain les ions are assessed in order to diagnose AD.

Cortical atrophy is a key trait of the AD brain that is typically diffuse and reasonably comparable throughout the cerebral he mispheres rather than being conspicuous in certain lobes or on one side of the brainIn certain fronto-temporal lobar degenerations, for example. Although it is not always the case, fresh brain weight is typically below the adult normal range of 1,200–1,400g. In exceptional cases, it may even be above the upper range of normal. Cortical atrophy, which manifests as thinning of the cortical ribbon, is typically accompanied by ventricular system enlargement, also known as hydrocephalus ex-vacuo, and occasionally by subcortical white matter shrinkage, atrophy, and/or pallor. Two distinct patients' coronal slices of (fixed) brains, one with and one without dementia, are at similar coronal levels (close to the caudate nucleus' head there is less cortical thinning. A progressive decline in cognitive function is the hallmark of Alzheimer's disease, which accounts for 70% of all dementia cases and is the sixth most common cause of death. Alzheimer's disease also manifests as confusion, poor judgment, annoyance, withdrawal, and hallucinations. Seizures, Parkinsonian symptoms, myoclonus, increased muscular tone, incontinence, and mutism might occasionally happen.3. Patients should receive primary care in order to identify and monitor their illness, even if they may face

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different diagnostic and treatment obstacles. This aids in the early detection and identification of Alzheimer's disease, which eventually results in the provision of psychosocial support and symptomatic medication therapy

**AD's World Wide Economy**

1.By 2050, there will likely be 106.8 million instances of AD worldwide, up from 26.6 million in 2006.9. In 2010, the estimated global expenses of dementia amounted to US$604 billion, or 1% of global GDP. Less than 1% of global expenses were incurred by low-income nations (although they accounted for 14% of dementia prevalence), 10% by middle-income nations (though they accounted for 40% of dementia prevalence), and 89% by high-income nations (though they accounted for 46% of dementia prevalence). Just two regions accounted for around 70% of the global costs.

North and Western Europe. The significantly lower cost per North person in lower-income countries—US$ 868 in low-income countries, US$ 3,109 in lower-middle-income countries, US$ 6,827 in upper-middle-income countries, and US$ 32,865 in high-income countries—explains these disparities.6. While the percentage share of direct medical costs (15%) is far smaller, the majority of costs in high-income nations are attributed to informal care (45%) and formal social care (40%). Informal care expenditures—that is, unpaid care given by family members—dominate in low- and lower-middle-income nations, while direct social care costs are negligible. According to the 2012 WHO report "Dementia: a health priority.10," shifting population demographics in various LMIC may result in a decrease in the readily available extended family members in the ensuing decades.

**Clinical Standards**

Based on the criteria of the Alzheimer's Disease and Related Disorders Association (ADRDA) and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the diagnosis of Alzheimer's disease is classified as probable (typical clinical syndrome without histological confirmation), definite (clinical diagnosis with histological confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histological confirmation).A decline in other areas of cognition, like anomia and reduced executive functioning, may be the major symptoms to be detected, according to the new guiding principle, which expands the definition of Alzheimer's dementia beyond memory loss as its principal symptom. It is possible to use biomarkers to improve diagnosis specificity.

The process of making a clinical diagnosis of Alzheimer's disease is explained as follows: the patient's history and the most crucial details regarding any prior illnesses are obtained from an informant in the first phase. The assessment of mental health and a confirmatory cognitive function test are part of the second phase. The physical examination, which is the third and most crucial step, should concentrate on neurological and vascular symptoms and be supported by investigations. The method of diagnosing dementia involves two steps. 13.First and foremost, it's critical to distinguish dementia syndromes from other illnesses that downplay them, such as mild cognitive impairment, delirium, and depression. Second, diagnosing the dementia subtype is crucial when dementia syndrome has been identified since it aids in selecting the best course of treatment.

**Pharmacotherapeutics of AD**

For the treatment of AD-associated dementia, there are currently just four approved and marketed medications, and their effectiveness is restricted. Three of these medications—donepezil, galantamine, and rivastigmine—act on cholinergic pathways in the central nervous system (CNS). All three medications exhibit anticholinesterase properties, while the natural alkaloid galantamine functions as an allosteric modulator at nicotinic acetylcholine receptors.

These medications are licensed for mild to severe dementia and are now accessible in generic forms. However, based on the findings of cognitive testing, they are frequently prescribed to patients in early stages of predementia who have considerable progressive memory deterioration. The most recent medication approved for AD in the US is memantine, which is noteworthy for being the first to target the glutaminergic pathway and the N-methyl-d-aspartate (NMDA) receptor.

A pathophysiological mechanism in AD has recently been linked to excess glutamate at excitatory synapses with accompanying cytotoxicity, which may be caused by reduced glutamate absorption from microglia. In a mouse model of the illness, glutaminergic regulation influences dendritic spine clustering.

Along with their approved indications, memantine and donepezil are both licensed medications used in monotherapy to treat AD symptoms.43 Memantine and donepezil both exhibit different and complementary modes of action, and when taken together, they provide the patient with extra advantages. Data from clinical studies conducted on healthy participants offered preliminary evidence that memantine and donepezil might be administered together without risk. In patients with AD, memantine exhibits a good safety profile when used in conjunction with steady ChEI treatment.

**Non-pharmacological therapy of AD**

Alzheimer's patients' quality of life (QOL) can be enhanced by non-pharmacological therapy (NPTs).

A small number of well-conducted randomized controlled trials have demonstrated that different forms of stimulation therapy can help people with AD with their **caues.** cognitive symptoms. These trials also suggest that cholinesterase inhibitor therapy may have additional benefits. Age-related sleep and wakefulness issues could be caused by a lowering of circadian rhythm amplitudes. Sleep and cognitive functioning in older adults and Alzheimer's patients seem to be improved by non-pharmacologically modifying circadian rhythms through a variety of environmental

**Sleep**

disturbance appears to be a contributing factor to the pathogenesis of Alzheimer's disease. Inappropriate sleep causes amyloid-β (A β) to build up, which may cause memory loss in the early stages and eventually lead to AD. Numerous studies have revealed that sleep patterns either directly or indirectly

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impact Alzheimer's disease. Aβ, AD, and non-rapid-eye-movement (NREM) sleep disturbance are associated with a probable mechanism. A new mechanism that links cortical Aβ to poor hippocampus-dependent memory consolidation is disruption of NREM sleep. Appropriate sleep appears to be a novel treatment focus in older age, offering therapeutic and anticipatory compensation.

As a non-invasive biomarker of Aβ pathology, AD risk, and AD pathophysiological development, the disturbance of NREM sleep physiology may have diagnostic value. There is evidence linking sleep disturbance to the development of AD; this disturbance is controllable and may be prevented or treated therapeutically.
Both direct and indirect biological factors influencing brain health have been connected to physical and cognitive activity. Details on the kind, level of intensity, duration, and mix of interventions must be investigated in future studies.

**Music Therapy**
While some research have shown that music therapy can help with the behavioral and psychological symptoms of dementia, the majority of these investigations are small and uncontrolled. For moderately severe and severe AD, music therapy is a safe and efficient way to reduce agitation and anxiety. Potential problems with diagnosis, selecting therapeutic targets, developing drug candidates, and designing clinical trials result from both successes and failings in our understanding of the pathophysiology of Alzheimer's disease. Numerous in vitro and in vivo investigations are still being conducted, but we must prioritize finding a suitable treatment for Alzheimer's disease, therefore this advancement in the creation of medications for the condition needs to be re examined. Clinical trial research often gives us

In addition to providing new insights into Alzheimer's disease treatment, music aids in the research of pharmacological interaction patterns rather than focusing on a particular potential medication target. We are getting closer to creating the best possible pharmaceutical strategy for treating Alzheimer's disease thanks to a number of ongoing randomized controlled trials that show encouraging results and provide a means of fostering greater cooperation between pharmaceutical companies, basic researchers, and clinical researchers.

**Potential Herbal Drugs For AD**
There are common traditional Indian botanicals that may help treat neurological conditions including dementia and Alzheimer's. Ayurvedic rasayana medications are abundant in immunomodulatory and antioxidant compounds. Some of these medications have already been shown to have considerable antioxidant activity. Since the delicate balance between oxidants and antioxidants is disrupted in most illnesses,

You could consider their primary mode of action to be their capacity to scavenge free radicals or to activate oxidant defenses of cells. Ashwagandha, Brahmi, Mandukaparni, Shankapushpi, Vacha, Jatamansi, and Jyotshmati are just a few of the numerous plants that fall within the Rasayana plant category. These herbs are categorized as brain tonics or rejuvenators since they are unique to brain tissues. In addition to the aforementioned, our labs have reported that a number of Rasayana medications have a positive impact on memory impairments and are recommended for a possible function in dementia and other neurological disorders. They may also be useful in AD.

As a shrub, ashwagandha (Withania somnifera) belongs to the solanaceae family. It is regarded as an adaptogen, a non-toxic drug that engages the immunological and endocrine systems to restore physiological processes against long-term stress. By increasing neurite outgrowth, ashwagandha may aid in the restoration of damaged neural circuits

**Brahmi**
Since ancient times, Brahmi (Bacopa monniera; family: Scrophulariaceae) has been utilized as a valuable brain tonic to improve cognitive function, reduce stress in anxiety, and rejuvenate the intellect. According to numerous research, this medicinal herb can be used to treat mental and neurological diseases since it functions as a nervine and mental tonic16.
4. Chandan Chandan, a member of the Santalaceae family (Santalum album). According to Siddha, this plant has the ability to improve cognitive function and memory. Licorice has a strong memory-boosting effect and helps people with scopolamine-induced dementia learn and remember things better.

**Haldi**
The majority of chronic disorders, including as autoimmune, metabolic, pulmonary, cardiovascular, neurological, and neoplastic conditions, are treated with haldi (Curcuma longa).16 One herbal medication with therapeutic potential for AD is curcumin. When given to a mouse model of AD17, curcumin, the principal chemical component of haldi or turmeric, reduced the blood Aβ level and lessened the load of Aβ in the brain. This effect was mostly observed in the neocortex and hippocampus of the AD animal model. Curcumin penetrates the blood-brain barrier, prevents Aβ plaques from forming, destroys preexisting Aβ fibrils, and stops them from extending. Curcumin therapy has a greater therapeutic impact and can restore the distorted neuritic morphology found close to plaques

**Symptoms**
- ❖ Memory loss is the key symptoms of Alzheimer disease
- ❖ Depression
- ❖ Loss of interest in activities
- ❖ Anger or aggression
- ❖ Anxiety
- ❖ Mood swings.

**Causes /Risk Factors**
- ✓ Age
- ✓ Family history
- ✓ Genetics
- ✓ Down syndrome
- ✓ Excessive alcohol consumption

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✓ Lifestyle and her health

**Prevention**

1.Exercise Regularly
2.Eat Healthy
3.Manage Chronic Condition
4. Reduce Stress
5. Blood Pressure Management
6. Mental Stimulation

**Types**

1.Earlyonset
The kind is less prevalent than let on set, and symptoms start to show before the age of 60. and frequently connected to chromosome 1 defects
2. Arriving late to the set
This is the most prevalent disease that affects persons 65 and older.

## SYMPTOMATIC TREATMENT OF AD

➢ **Cholinesterase Inhibitors**

The cholinergic hypothesis states that AD results from a decrease in the manufacture of acetylcholine (ACh). One of the treatment approaches that improves cognitive and neural cell function is to raise cholinergic levels by blocking acetylcholinesterase (AChE). Acetylcholine breakdown in synapses is inhibited by AChEIs, causing ACh to continuously accumulate and cholinergic receptors to become activated. The first FDA (Food and Drug Administration)-approved cholinesterase inhibitor medication for the treatment of AD was tacrine (tetrahydroaminoacridine), which works by raising ACh in muscarinic neurons. However, it was taken off the market right away because of a high rate of adverse effects, such as hepatotoxicity, and a lack of benefits, which were noted in multiple trials. Later on, a number of AChEIs were released, including donepezil, and areThe cholinergic hypothesis states that AD results from a decrease in the manufacture of acetylcholine (ACh). Increasing cholinergic levels is currently being used to treat AD symptoms. Increasing choline reuptake and, consequently, acetylcholine production at the presynaptic terminals is another tactic that could aid in the treatment of AD.

The choline transporter (CHT1), which provides choline for the manufacture of ACh, can be targeted to do this. The future of AD treatment may involve creating medications that can raise CHT1 at the plasma membrane. It includes the following medications:

**Donepezil**

The most used medication for treating AD is donepezil, a second-generation AChEI and derivative of indanonebenzylpiperidine. Acetylcholine hydrolysis is inhibited by donepezil's reversible binding to acetylcholinesterase, increasing the amount of ACh at synapses. The medication has minor and temporary cholinergic side effects that are associated with the neurological and gastrointestinal systems, although they are well tolerated. It should be mentioned that donepezil is used to treat AD symptoms, such as enhancing behavior and cognitive, without changing the course of the disease.

**Rivastigmine**

The mechanism of action of rivastigmine, a pseudo irreversible inhibitor of AChE and butyrylcholinesterase (BuChE), is to bind to the anionic and estearic sites of AChE, hence blocking ACh metabolism. Although BuChE is mostly present in glial cells and has only 10% of AChE activity in the normal brain, its activity can range from 40% to 90% in the AD brain while ACh activity is also decreased. This shows that BuChE action could be a sign of moderate to severe dementia.Rivastigmine is referred to as a pseudo-irreversible because it dissociates more slowly than AChE. AChE and BuChE metabolize it at the synapse. When AD is mild to severe, the medication is administered. The majority of AD patients experience swallowing issues and memory loss, which impact their

**Memantine**

AchE inhibitors are not what this is.It functions by preventing the effects of glutamate, a neurotransmitter that is present in the brain in excess. It used to serve AD or moderate it. NMDA, or N-methyl d-aspartate. Ach-producing cells are destroyed by a number of physiological events in AD, which lessens cholinergic transmission in the brain. Reversible, irreversible, and pseudo-reversible acetylcholineses22terase inhibitors (AChEIs) work by preventing the breakdown of ACh by cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)).

## PATHOPHYSIOLOGY

An accumulation of aberrant neuritic plaques and neurofibrillary tangles in the brain is a pathological hallmark of Alzheimer's disease. Neurons, especially cholinergic neurons in the neocortex and basal forebrain, are lost in conjunction with these pathogenic alterations.

In addition to subcortical nuclei like the serotonergic dorsal raphe, noradrenergic locus coeruleus, and cholinergic basal nucleus, neuronal loss and/or pathology can be observed in the entorhinal cortex, hippocampus, amygdala, and cortical association areas of the frontal, temporal, and parietal cortices. There is a pattern to the way tangles get deposited.

## CONCLUSION

With an emphasis on both symptom management and possible disease modification, pharmacological approaches for Alzheimer's disease have undergone significant change.The prevalence and course of Alzheimer's disease (AD) in Arabian populations are influenced by distinct genetic, environmental, and cultural factors, as is now understood.

AD is a condition that has been shown to be challenging and demanding.It is caused by lifestyle issues and environmental factors.Alzheimer's disease is a terrible illness that needs immediate care. Even while there has been progress, there are still many obstacles to overcome. Improving diagnosis, care, and treatment requires ongoing research, creativity, and cooperation.We must give research, early detection, and compassionate care top priority as our knowledge of its causes, symptoms, and development grows. By doing this, we can help

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people impacted, provide support to their families, and work toward developing efficient treatments and, eventually, a cure.

## SUMMARY

Which is the sixth most common cause of death. By 2050, there will likely be 106.8 million instances of
AD world wide, upfrom26.6millionin2006.

AD is Seventy percent of dementia cases are caused by Alzheimer's disease (AD), a condition that has been shown to be challenging and demanding.It results from changes in lifestyle and environmental factors. In addition to current pharmacotherapies, biomarkers, and therapeutic targets, the quest for comprehensive AD therapy is ongoing. Nonetheless, it is commendable to combine medicine with non-pharmacological therapeutic methods.

## THE FUTURES SCOPE

Numerous areas of attention are emerging in the promising field of research. One important field is biomarker development, which seeks to create trustworthy and efficient biomarkers for Alzheimer's disease monitoring, diagnosis, and early detection. This includes analytical and clinical validation of biomarkers, such as those measured with digital technology

1) Research is being done on personalized medicine techniques, which center on customized therapies based on personal traits including genetic profiles and lifestyle choices.
2) The effects of lifestyle interventions on the prevention and treatment of Alzheimer's disease are being investigated. Examining how nutrition, exercise, and social interaction affect cognitive health is part of this.
3) Strategies for neuroprotection and regeneration seek to prevent harm to neuronal cells and encourage their regeneration. This covers studies on immunotherapy, gene editing technology, and stem cell therapies.

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