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# Clinical Pharmacy Newsletter

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## Prevention of Alzheimer's disease: Lessons learned and applied

### Introduction

Alzheimer's disease (AD) affects more individuals across the globe, with substantial costs to individuals with AD, families, and society. Over the past 25 years, only five symptomatic medications have met their primary clinical trial endpoints in Phase III clinical trials and successfully come to market; of these, four are still available. Since 2003, every symptom- and disease-modifying agent has failed in Phase II or III trials because of challenges with safety or efficacy. This led to a bold initiative put forth in the National Alzheimer Plan Act to develop a disease-modifying treatment (DMT) by 2025. Two important concepts are associated with success to reach this target date. First, only medications that have already entered Phase II testing can make it to market by 2025.[2] Second, if a DMT were available by 2025, to complement the efforts to develop a DMT for individuals with symptomatic AD, a concerted effort is underway to initiate preventive measures in asymptomatic individuals.

Whether AD can be prevented? - A large number of modifiable (e.g., exposures, lifestyle and social habits) and nonmodifiable (e.g., age, sex, genetics) risk factors have been identified. Recent revisions to the clinical criteria for AD and mild cognitive impairment (MCI) helped clarify the role of biomarkers in defining the pathological cascade, and the addition of research criteria for presymptomatic disease sets the stage for better modeling of the preclinical and prodromal stages of disease.

Table 1: Alzheimer's disease risk and protective factors

| *Risk Factors (Nonmodifiable)* | *Risk Factors (Modifiable)* | *Protective factors (Modifiable)* |
|---|---|---|
| Age<br>Sex<br>Family history<br>Apolipoprotein E ε4 allele* | Diabetes mellitus and insulin resistance<br>Obesity<br>Metabolic syndrome<br>Hypertension<br>Hypercholesterolemia<br>Cerebrovascular disease<br>Depression<br>Psychological and physiological stress<br>Traumatic brain injury<br>Sleep disordered breathing<br>Smoking<br>Alcohol abuse | Cognitive reserve and mental activity<br>Educational attainment and lifelong learning<br>Cognitive leisure activities<br>Physical activity and exercise<br>Social engagement<br>Mindfulness and wellness activities<br>Optimism and purpose in life<br>Diet<br>Omeage-3 intake |

*Apolipoprotein E is the major risk gene; a number of other minor risk genes have been identified.

Efforts developing and validating fluid (blood and cerebrospinal fluid) and imaging biomarkers make it possible to explore underlying pathological changes in amyloid, tau, dopamine transport, inflammation, signaling pathways, and in the future, alpha-synuclein and TDP-43 in symptomatic, prodromal, and presymptomatic individuals. Advances in genetic, epigenetic, and "omic" (e.g., proteomic, lipidomic, metabolomic) approaches will

These efforts have a great potential for pharmaceutical and nonpharmacological approaches, with earlier identification of at-risk individuals, expanding opportunities for faster and earlier diagnoses, better stratification of at-risk individuals, higher enrollment into randomized clinical trials (RCTs) by reducing screen failure rates, and eventually more-effective treatments.

**Pharmacological approaches to prevention:**
A number of prevention studies are ongoing in sporadic and autosomal-dominant forms of AD. One such study is the anti-amyloid treatment in asymptomatic Alzheimer's study, which recruited individuals aged 65 to 86 with normal cognitive function but positive AD biomarkers (amyloid deposition according to positron emission tomography). These individuals are followed for 3 years of treatment with an anti-amyloid monoclonal antibody.

The Alzheimer Prevention Initiative will study individuals aged 60 to 75 with normal cognition who have two copies of the apolipoprotein E e4 allele, putting them at high risk of AD. These individuals are followed for 2 years of treatment with a different anti-amyloid monoclonal antibody. The TOMMORROW Study will enroll individuals aged 65 to 83 with normal cognition who have a polymorphism of the TOMM40 gene that is associated with greater risk of AD. Individuals are followed for 5 years of treatment with pioglitazone, an anti-diabetes drug. In parallel to these trials in sporadic cases with enhanced risk, trials are ongoing in individuals with autosomal-dominant forms of AD, including the Alzheimer Prevention Initiative and Dominantly Inherited Alzheimer Network—Treatment Unit using monoclonal antibodies. A particular advantage of the trials in familial AD is that age of onset is predictable so that, if a DMT effect exists, it is more likely to be detected. A potential disadvantage of these trials is that the results may not be generalizable to the much more common sporadic forms in which risk factors other than genetics may predominate.

**Lifestyle modification interventions**
A number of modifiable risk and preventive factors for AD have been described in Table 1. The most difficult of these factors to address is diet because it is highly dependent on income and access to fresh foods. In a 16-year observational study of 949 individuals using the Lifestyle for Brain Health (LIBRA) measure of modifiable risk factors, a 1-point increase in LIBRA score was associated with a 19% greater risk of dementia. In a meta-analyses of 19 studies, cognitive leisure activities, including crossword puzzles, card games, computer use, arts and crafts, life-long learning, group discussions, and music, had a protective effect (odds ratio (OR) = 0.58). In addition, physical activities may lead to a 20% to 65% risk reduction depending on the type and intensity of activity through mechanisms involving lower vascular disease risk, better respiratory function, stimulation of trophic factors, and lower oxidative stress and inflammation. Objective measurement of midlife vascular risk factors demonstrated greater risk of dementia in late life. In a study of 2,000 individuals aged 71 to 78, work-related stress increased the risk of MCI (OR = 1.38), dementia (OR = 1.53), and AD (OR = 1.55).

**Ongoing prevention initiatives**
The Innovative Midlife Intervention for Dementia Deterrence trial is examining 11 identified risk factors (e.g., diabetes, hypertension, renal) that account for half of the attributable risk and has enrolled 600 individuals to participate in an on-line education intervention. The largest initiative to date is the FINGER study, enrolling 1,260 individuals in an educational intervention that includes modules in diet, exercise, cognitive training, and vascular risk reduction. Overall between-group differences were statistically significant for global cognition,

**Precision medicine approaches to Prevention**

Up to 30% of AD cases may be preventable through modification of risk factors and behavioral changes to mitigate the effect of those risk factors that are not modifiable. There is an ongoing debate as to whether the current evidence base is sufficient to initiate prevention programs because it is difficult to prove causation from observational studies, and it is difficult to pool multiple RCTs because of differences in study design, measurements used, and anticipated outcomes. Although a well-balanced, healthy lifestyle may be the cornerstone of disease prevention and brain health, each risk factor (vascular, lifestyle choices, psychosocial) may both act independently and potentiate the effects of each other. Therefore, a prevention initiative needs to be multimodal and tailored to address individual risks. Because AD is heterogeneous in terms of risk factors, age of onset, presentation, progression, and pathology burden, designing a study to treat individuals as a homogenous population requires large sample sizes (thousands to tens of thousands) to be followed for long periods of time (years to decades).

Many prevention RCTs use time-to-event analytical strategies to demonstrate a DMT effect. Such designs are optimal when anticipated treatment effects remain constant over time, but in the case of dementia prevention, this is unknown. Thus, time-to-event analyses such hazard ratios may not be the best way to model effects, particularly if the detectable signal is a late effect of the intervention. This results in large study costs, staff burden, and participant burden. In the absence of robust biomarkers that mark disease onset and progression, rather than just the presence of pathology, RCT design will remain a challenge. Barriers to prevention studies include limited understanding of the real relationship between dementia risk factors and the effect of risk reduction; complexity of the effect of life course on dementia risk factors; lack of standardization of study design, definitions, and outcomes; difficulty translating RCT findings into real-world practice; cultural and social barriers to implementation; lack of research capacity to enroll large research cohorts for long periods of time; and pervasive social stigma associated with AD.

**Discussion**

There is increasing evidence that multiple medical conditions increase the risk of neurodegeneration and subsequent development of dementia. It is also becoming clear that the majority of these risk factors act in amyloid- and tau-independent ways. Trials testing the amyloid hypothesis (β- and γ-secretase inhibitors, anti-aggregation medications, mono- and polyclonal antibody approaches), anti-inflammatory agents, and early-phase anti-tau therapies have failed to meet outcomes or have been discontinued because of safety concerns. In all likelihood, efforts to prevent cognitive decline and development of dementia may be more successful when they are multimodal and directed to at-risk individuals based on their personal health profile, rather than using "one-size-fits-all" approaches. The detection of and interventions addressing root causes may offer novel approaches to diagnosing, treating, curing, or preventing AD. AD offers a large array of potentially modifiable risk factors (lifestyle, exposure, environment, comorbid disease) that are excellent targets to personalize the approach to medical care.

Precision medicine approaches specifically target the heterogeneity of AD by identifying person-specific risk factors and applying a customized intervention directed against this risk profile. Even if these precision approaches do not cure or prevent AD, removing other pathways to neurodegeneration may greatly improve the likelihood that amyloid- or tau-specific

# EVENT CORNER

January To March 2018

REPORT

**Conferences Attended by Faculty**

Dr. S Ponnusankar, Dr. K P Arun, Ms. Deepalakshmi M, Dr. G K Sadagoban, Dr. Swathi Swaroopa B, Dr. Keerthana C, Dr. Aneena Suresh, Dr. Khayati Moudgil and Mr. Jayakumar C. attended One Day Workshop on "Research and Publication thought process for Faculty" on 17.01.2018 at JSS College of Pharmacy, Ooty organized by Pharmacy Education Unit.

Dr. S Ponnusankar, Dr. K.P. Arun, attended Indian Pharmaceutical Association – National Convention 2017 –18, Organized by Indian Pharmaceutical Association – Tamilnadu Branch at BS Abdur Rahman Crescent Institute of Science and Technology, Chennai on 10-11th February 2018.

Dr. K.P. Arun, Ms.M..Deepalakshmi, Mr. Vishwas H N, Dr. GK Sadagoban, Dr. Swathi Swaroopa, attended a Workshop on "Research Methodology & Biostatistics using SPSS Organized by Centre for Clinical Research Excellence (CCRE)-Clinical Development Services Agency (CDSA) in Collaboration with Dept. of Community Medicine, JSSMC, Mysore & JSSCP, Ooty at JSSCP Ooty on 16th & 17th February, 2018.

Dr. Khayati Moudgil attended the CLINPHARMA SUMMIT Module-2Advanced Practical Skills in Clinical Pharmacy Service Organized by Aster MIMS, Calicut, on 11th March 2018

Ms. Roopa BS attended the Life and Liberty, Fostering Safe Work Place, Organized by Internal Complaints Committee of JSS Academy of Higher Education & Research, Mysuru at Gowrishankara Auditorium, JSS Dental College and Hospital, Mysuru on 27 March 2018.

**Research Awards / Recognitions**

Mr. Tenzin Tsundue PharmD got Best Oral Presentation at 3rd International Conference on Clinical Pharmacy, Organized by Dept of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal on 21.01.2018.

January To March 2018

REPORT

**Faculty as Resource Persons**

1. Dr. Anand Vijaya Kumar delivered a talk on Protocol approval process – for clinical trials, Dr. D Raja delivered a talk on Cochrane Systematic Review and meta-analysis, and Ms. Roopa BS delivered a talk on Systematic Review and Meta-Analysis at One Day Workshop on Research and Publication thought process for faculty organized by Pharmacy Education Unit on 17.01.2018.

2. Dr. G K Sadagoban delivered a talk on Pharmaceutical Care – An Overview Internal CME Program State Organizer at Sree Vidhyanikethan College of Pharmacy Tirupati, Andhra Pradesh on 11.01.2018.

3. Ms.M..Deepalakshmi recognized as Coordinator for All India Quiz 2018, Preliminary round Organized by Madras Medical College, Chennai in February 2018.

4. Dr. G.K. Sadagoban delivered a talk on ICT enabled Teaching – Learning is "Boon or Bane" National CME on "Teaching and Learning in Digital Era" Organized by JSS Academy of Higher Education & Research, Mysuru, Department of Anatomy on 9 March 2018.

September to December 2017

# Drug Profile: OZENOXACIN

**Class:**
**Quinolone Anti-biotic (Topical)**

**Indication:** Topical treatment of impetigo due to Staphylococcus aureus or Streptococcus pyogenes in adult and pediatric patients two months of age and older.

**Mechanism of Action:**
Ozenoxacin causes inhibition of bacterial DNA replication enzymes, namely DNA gyrase A and topoisomerase IV. Ozenoxacin has been shown to be bactericidal against *S. aureus and S. pyogenes organisms.*

**Dosage form and Administration:**
Ozenoxacin is available as a pale yellow colored Cream (1%). Each gram of cream contains 10 mg of Ozenoxacin. Drug has to be applied as a thin layer topically to the affected area twice daily for 5 days. Affected area may be up to 100 $cm^2$ in adult and pediatric patients 12 years of age and older or 2% of the total body surface area and not exceeding 100 $cm^2$ in pediatric patients less than 12 years of age.

Dosing in Renal Impairment: No dosage adjustment is required for patients with mild, moderate, or severe renal impairment.

Dosing in Hepatic Impairment: No dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment.

**Pharmacokinetics:**
Four pharmacokinetic studies were conducted in 110 patients utilizing varying strengths of ozenoxacin cream, up to 2%. Three studies assessed systemic absorption in healthy subjects and in subjects with impetigo.

These studies were conducted with either single or repeated application of up to 1 g ozenoxacin cream to intact or abraded skin (up to 200 cm2 surface area). No systemic absorption was observed in 84 of 86 subjects, and negligible systemic absorption was observed at the level of detection (0.489 ng/mL) in 2 subjects.
Plasma protein binding of [14C]-ozenoxacin was moderate (~80 to 85%) and did not appear to be dependent on concentration. Tissue distribution studies have not been performed in humans.
Ozenoxacin was not metabolized in the presence of fresh human skin discs and was minimally metabolized in human hepatocytes. Studies have not been investigated in humans due to the negligible systemic absorption observed in clinical studies.

**Adverse Reactions:**
Rosacea and Seborrheic dermatiti) were reported in 1 adult patient treated with ozenoxacin. Apart from these, none of the ADRs were reported from studies.

**Contraindications:**
None

**Precautions:**
The prolonged use of Ozenoxacin may result in overgrowth of non-susceptible bacteria and fungi. If such infections occur during therapy, immediately the drug should be discontinued.

**Drug Interactions:**
None Reported till date

**Storage:** The cream has to be stored in Room temperature. (20ºC - 25ºC)

**Reference:**
1) https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm537040.htm

September to December 2017

# RESEARCHERS DISCOVER ALZHEIMER'S TREATMENT WHILE TRYING TO CURE DIABETES

Developing new treatments for ailments can be a tedious and frustrating process for scientists. Often, newly developed drugs just don't work the way they were intended, falling short of expectations and leading to a dead end. But other times, a drug developed for one purpose turns out to be even more effective at treating something completely different. That appears to be exactly what is happening with a new class of drug originally developed for the treatment of Type 2 diabetes, but which has recently been shown to have a drastic benefit in mice with Alzheimer's.

The new drugs, which are classified as "triple agonist" (because they work in three ways), were tested on mice which were developed to express genes linked to Alzheimer's. The animals were already exhibiting many of the symptoms associated with the disease, including compromised memory and difficulty learning, but showed dramatic improvement in their brain function after receiving the unique treatment.

The treatment "holds clear promise of being developed into a new treatment for chronic neurodegenerative disorders such as Alzheimer's disease," explains Christian Holscher, lead researcher of the study. The research was published in Brain Research.

According to the study, the triple-acting treatment is thought to work against Alzheimer's disease by protecting nerve cells, reducing amyloid plaques in the brain (which have been linked to Alzheimer's) and reducing inflammation while slowing nerve cell degradation. Mice that received

Discovering a potential new treatment for a devastating disease like Alzheimer's is fantastic news, but the fact that the drug was initially intended to treat Type 2 diabetes isn't just a coincidence. Type 2 diabetes has been linked to Alzheimer's in the past and the two often go hand in hand in older individuals. "Insulin desensitization has also been observed in the Alzheimer's disease brain," the researchers explain in a press release."The desensitization could play a role in the development of neurodegenerative disorders as insulin is a growth factor with neuroprotective properties."

The treatment has not yet been approved for Alzheimer's patients and has only been demonstrated in these early trials with mice. Further research is most certainly warranted and if we're lucky, we might actually have a go-to solution for the disease sooner rather than later.

## Recently approved drugs by FDA

| S.N | Drug | Indication | Date of approval |
|---|---|---|---|
| 1. | Lutathera (lutetium Lu 177 dotatate) | To treat a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropan-creatic neuroendocrine tumors (GEP-NETs). | 1/26/2018 |
| 2. | Biktarvy (bictegravir, embitcitabine, teno-fovir alafenamide) | To treat infection in adults who have no antiretro-viral treatment history or to replace the current antiretroviral regimen | 2/7/2018 |
| 3. | Symdeko (tezacaftor; ivacaftor) | To treat cystic fibrosis in patients age 12 years and older | 2/13/2018 |
| 4. | Erleada (apalutamide) | To treat a certain type of prostate cancer using novel clinical trial endpoint | 2/14/2018 |
| 5. | Trogarzo (ibalizumab-uiyk) | To treat HIV patients who have limited treatment options | 3/6/2018 |
| 6. | Ilumya (tildrakizumab) | To treat adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy | 3/20/2018 |

**REFERENCE:** https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm592464.htm

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