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ANALYSIS OF MEDICATION AND PHARMACOLOGY FOR ALZHEIMER'S DISEASE COMMONLY USED IN PAKISTAN: A TRANSLATIONAL STUDY

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Abstract:

Introduction and objective of the study: *Alzheimer's disease (AD) is the most common form of dementia accounting for 60–80% of dementia diagnosis and affects nearly 50 million people worldwide. The worldwide number of affected individuals is expected to reach 66 million by 2030, and 131 million by 2050 as the number of older adult's increases. Due to the large number of published articles in biomedical research of AD, we refer to more recent comprehensive reviews written by domain experts and supplement these with other findings. The basic aim of the study is to find the therapeutic medicines used for the AD in Pakistani environment.* ***Methodology of the study:*** *This study was conducted at different hospitals of Pakistan. Basically, we collect the data from doctors and patients both because we want to find the therapeutics of AD in local population of Pakistan. This study was completed almost in 3 months during 2017. We conduct the interviews and questionnaire for analysis.* ***Results:*** *Measuring and, possibly, controlling space- and time-scaled adaptive and compensatory responses occurring during AD will represent a crucial step to achieve the capacity to substantially modify the disease course and progression at the best suitable timepoints, thus counteracting disrupting critical pathophysiological inputs. This approach will provide the conceptual basis for effective disease-modifying pathway-based targeted therapies.* ***Conclusion:*** *It is concluded that there are no clear and perfect medication for AD. The current diseased approach for AD consists of optimizing modifiable risk factors to reduce and delay symptom onset as well as symptomatic treatment after disease onset.*

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INTRODUCTION:

Alzheimer's disease (AD) is the most common form of dementia accounting for 60–80% of dementia diagnosis and affects nearly 50 million people worldwide. The worldwide number of affected individuals is expected to reach 66 million by 2030, and 131 million by 2050 as the number of older adult's increases [1]. One in 10 people over age 65 and every third person over age 85 in the US has a diagnosis of AD. The global financial toll of dementia was estimated to be 818 billion US dollars in 2015, an increase of 35% since 2010 and this cost is expected to further rise together with the prevalence of AD. The majority of the costs are related to family and social care of patients, rather than medical care. About 5% of all AD patients show cognitive symptoms before age 65 and are classified as early onset Alzheimer's disease (EOAD). Patients showing clinical symptoms after age 65 are classified as having late onset Alzheimer's disease (LOAD)[2]. Here, we provide a summary of the clinical, neuropathological, fluid, and imaging biomarkers of AD along with a more comprehensive review of genetic findings in both Mendelian and sporadic forms of AD [3]. We discuss how genetic analysis as applied in Mendelian randomization (MR) may be helpful in validating causality of modifiable risk factors that could advance preventive measures. Moreover, genetic data may be useful to facilitate precision medicine. The goal of precision medicine is to integrate clinical, genetic, and life style data to enable clinicians to efficiently and accurately predict the most appropriate course of action for a patient. We emphasize the ways genetics may facilitate precision medicine in AD: (1) identifying at risk individuals through risk prediction, (2) improving diagnostic precision, and (3) expediting the discovery of targetable disease mechanisms for drug development [4].

Background and aim of the study

Due to the large number of published articles in biomedical research of AD, we refer to more recent comprehensive reviews written by domain experts and supplement these with other findings [5]. The basic aim of the study is to find the therapeutic medicines used for the AD in Pakistani environment.

METHODOLOGY OF THE STUDY:

This study was conducted at different hospitals of Pakistan. Basically, we collect the data from doctors and patients both because we want to find the therapeutics of AD in local population of Pakistan. This study was completed almost in 3 months during 2017. We conduct the interviews and questionnaire for analysis. We included publications of the Mendelian AD genes as well as publications that were referred and curated by the National Human Genome Research Institute-European Bioinformatics Institute (NHGRI-EBI) Catalog of published genome-wide association studies (GWAS Catalog). In addition, we included high-quality association studies reporting rare variants that meet the "analytically rigorous" criteria for GWAS (9) or are otherwise statistically thorough.

Statistical analysis

Unconditional logistic regression was used to find out the odds ratios (ORs) and 95% confidence intervals for relations between blood transfusion, and risk of leukemia. Other variables, for example smoking, alcohol consumption, time of blood transfusion and family history, did not result in material changes in the observed associations. All *P* values presented in the results are two-sided, and all analyses were performed by using SAS software.

RESULTS:

Biomarkers for AD

To provide early and accurate diagnosis of AD, extensive efforts have been made into developing sophisticated methods to assess pathology in the living human brain. However, to date, no test or combination of tests that could accurately diagnose AD is available for broad clinical use outside of AD research centers[6]. CSF levels of Aβ42, tau, and hyperphosphorylated tau (ptau) as markers for amyloid, neuronal injury, and tangles, respectively, have been the main fluid biomarkers used in AD research. In CSF of AD patients, a decreased level of Aβ42 has been consistently found. Interestingly, a reduction of CSF Aβ42 had been shown to correlate with brain atrophy in non-demented elderly indicating a potential preclinical stage [7].

Drugs analysis

We collect the data and form a precise table regarding medications which are used for the therapeutic approach and medication of AD. (Table 01).

Table 01: Drugs used for AD

CR Best Buy	Drug/Strength/Form	Brand	Average Monthly Cost [2]	Frequency of Use Per Day [3]
	Donepezil 5 mg tablet	Aricept	$363	One
	Donepezil 5 mg tablet	Generic	$208	One
	Donepezil 10 mg tablet	Aricept	$352	One
	Donepezil 10 mg tablet	Generic	$203	One
	Donepezil 23 mg tablet	Aricept	$309	One
	Donepezil 5 mg dissolvable tablet	Generic	$240	One
	Donepezil 10 mg dissolvable tablet	Generic	$210	One
	Galantamine 4 mg tablet	Generic	$196	Two
	Galantamine 8 mg tablet	Generic	$183	Two
	Galantamine 12 mg tablet	Generic	$180	Two
	Galantamine 8 mg sustained-release capsule	Generic	$177	One
	Galantamine 16 mg sustained-release capsule	Generic	$179	One
	Galantamine 24 mg sustained-release capsule	Generic	$183	One
	Memantine 5 mg tablet	Namenda	$269	Two
	Memantine 10 mg tablet	Namenda	$266	Two
	Memantine 10 mg/5 mL oral solution	Namenda	$489	Two

Discussion:

The established AD associated genes exert pleiotropic functions across many molecular pathways. Several of these pathways stand out by providing insights for the disease mechanisms that may play a role in the etiology of AD. Major pathways include inflammatory response (ABCA7, CD33, CLU, CR1, MS4A, INPP5D, TREM2, PLCG2, PTK2B, and ABI3), lipid metabolism (APOE, CLU, ABCA7, and PLCG2), as well as endocytosis/vesicle-mediated transport (BIN1, PICALM, CD2AP, EPHA1, and SORL1). Other functional categories include regulation of cell cycle (RANBP2), oxidative stress response (MEF2C), and axon guidance (UNC5C) [7].

Table 02: Gene locus of AD

CHR	Region	Gene locus	Risk allele frequency	*P*-value	Risk allele OR
1	1q32.2	CR1	0.197	6.0E−24	1.18
2	2q13	RANBP2	0.08	4.0E−08	1.76
2	2q14.3	BIN1	0.409	7.0E−44	1.22
2	2q37.1	INPP5D	0.488	3.0E−08	1.08
5	5p15.1	FBXL7	0.92	5.0E−08	1.59
5	5q14.3	MEF2C	0.592	3.0E−08	1.08
5	5q31.3	PFDN1, HBEGF	0.5	7.0E−09	1.08
6	6p21.32	HLA-DRB5, HLA-DRB1	0.276	3.0E−12	1.11
6	6p21.1	TREM2	0.0063	2.0E−12	2.9
6	6p12.3	CD2AP	0.27	9.0E−09	1.11
6	6q25.1	MTHFD1L	0.07	2.0E−10	2.1
7	7p14.1	NME8	0.627	5.0E−09	1.08
7	7p12.1	COBL	0.991	4.0E−08	3.59
7	7q22.1	ZCWPW1	0.713	6.0E−10	1.1
7	7q35	EPHA1	0.662	1.0E−13	1.11
8	8p21.2	PTK2B	0.366	7.0E−14	1.1
8	8p21.1	CLU	0.621	3.0E−25	1.16
10	10p14	USP6NL, ECHDC3	0.4	3.0E−08	1.08
10	10p13	FRMD4A	0.028	1.0E−10	1.68
11	11p11.2	CELF1	0.316	1.0E−08	1.08
11	11q12.2	MS4A4E/MS4A6A	0.597	6.0E−16	1.11
11	11q14.2	PICALM	0.642	9.0E−26	1.15
11	11q24.1	SORL1	0.961	1.0E−14	1.30
13	13q33.1	SLC10A2	0.985	5.0E−08	2.68
14	14q22.1	FERMT2	0.092	8.0E−09	1.14
14	14q32.12	SLC24A4, RIN3	0.783	6.0E−09	1.1
17	17q22	BZRAP1	0.6	4.0E−08	1.09
17	17q25.1	ATP5H, KCTD2	0.09	4.7E−09	1.53
19	19p13.3	ABCA7	0.19	1.0E−15	1.15
19	19q13.32	APOE	0.15	2.0E−157	2.53
19	19q13.41	CD33	0.7	2.0E−09	1.1
20	20q13.31	CASS4	0.917	3.0E−08	1.14

A role of innate immunity and inflammation in AD etiology is independently supported by a large body of functional evidence. Among the risk genes from the immune pathways, TREM2 stands out with its high effect-size of AD risk. TREM2 stands for triggering receptor expressed on myeloid cells 2, a single-transmembrane protein expressed by monocytic myeloid cells. Both ApoE and Clusterin (encoded by CLU) are extracellular chaperons that prevent protein aggregation [8]. In addition, both bind to the microglial receptor TREM2 and thus may promote uptake of Aβ by microglia [9]. Studies on animal and human brains indicated that the TREM2 risk variant p.R47H impairs TREM2 detection of lipid ligands leading to microglia dysfunction. Observational studies have suggested that diabetes, mid-life obesity, mid-life hypertension, high cholesterol, and smoking are modifiable risk factors for AD. In terms of modifiable protective factors, education has been robustly shown to reduce AD risk. However, for many modifiable factors, no consistent pattern was found across studies. A recent comprehensive meta-analysis of 93 modifiable risk factors was conducted from 323 retrospective case/control and prospective cohort studies, which were selected after a systematic review of 16,906 publications. This study analyzed associations between AD risk and medical, dietary and occupational exposures as well as serum biochemistry, preexisting diseases, lifestyle, and psychological factors [10].

CONCLUSION:

It is concluded that there are no clear and perfect medication for AD. The current diseased approach for AD consists of optimizing modifiable risk factors to reduce and delay symptom onset as well as symptomatic treatment after disease onset.

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