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RESEARCH ARTICLE

Depression-inducing drugs and the frequency of depression in Alzheimer's disease and APOE ε4 carriers [version 1; peer review: 2 approved with reservations]

Dorothy Keine

3Prime Medical Writing, Durham, NC, 27703, USA

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Abstract

Background: Depression is associated with a greater risk of Alzheimer's disease (AD). Drug-induced depression is a well-known side effect of many medications and is more likely to occur in those who have a higher risk of depressive disorder.

Methods: A total of 292 individuals ages 65 and older were included in this dataset. Depressive symptoms were determined through self-reporting, the Short Form Geriatric Depression Scale (SF-GDS), prior diagnosis, or use of antidepressant medication. Depression-inducing drugs (DIDs) were identified using published references.

Results: Individuals took 11.51 (SD 8.86) medications and 1.16 (SD 1.27) DIDs per person. Depressed patients were more likely to be taking at least one DID (71.15% vs 28.85%, P value 0.005). Of the total population, 60.56% were taking at least one DID. Those with APOE ε4 had a significantly higher rate of depression than those without (69.12% vs 30.88%, P value 0.03).

Conclusions: DIDs are a substantial clinical, medical, and public health problem in older populations. DID consideration is important in populations with an increased risk or diagnosis of AD. Clinical decision support software (CDSS) provides a reliable method to help with DIDs.

Keywords

Depression, Alzheimer's, drug-induced depression, APOE, clinical decision support software

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1. **Carola G. Schipke** , Predemtec AG,
Gossau, Switzerland

2. **Marina Sagud** , University Hospital Center
Zagreb, Zagreb, Croatia

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Dorothy Keine (dorothykeine@gmail.com)

Author roles: Keine D: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

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Introduction

Alzheimer's disease (AD) is the most common form of dementia¹. It is a degenerative brain disease that eventually leads to death. Characteristic symptoms of the disease include difficulties with memory, language problems, agitation, and cognitive deficits that affect a person's ability to perform everyday tasks. As the disease progresses, the burden increases and the individual will need help with even basic activities of daily living¹.

An estimated 5.7 million people in the United States have AD, and over 35.6 million people are affected worldwide². This number is projected to grow as the population aged 65 and older in the USA is anticipated to increase from its current level of 53 million to 88 million by 2050. Today, the total US spending on AD is estimated to be \$277 billion¹.

Research now suggests that the brain changes associated with AD begin as much as 20 years before initial symptoms³. Individuals often begin to show early signs of cognitive decline when they develop mild cognitive impairment (MCI). A systemic review of 32 studies found that 32% of people with MCI will go on to develop AD within five years¹.

Like many chronic diseases, AD is not caused by one factor but instead develops because of multiple factors. Contributing factors include age, family history, the APOE $\epsilon 4$ gene^{4,5}, as well as modifiable lifestyle factors¹.

One factor often associated with AD is depression, both late-life (depression occurring after the age of 60 or 65) and recurring earlier-life cases. One in five individuals experience at least one depressive episode in their lifespan⁶, and it occurs more often in older populations^{2,7}. In 2009–2012, depression was estimated to affect more than 5% of all US adults⁸. Depression has also been found to be more common among women⁹. Many people with depression go undiagnosed and untreated⁸.

Evidence suggests that depression is preventable and treatable, and may be a modifiable risk factor for preventing or delaying dementia in later life⁷. Depression can lead to cognitive deficits in some individuals, sometimes referred to as "pseudodementia"^{2,10}. Older adults are at an even greater risk of developing pseudodementia^{9,11}.

It is currently unknown if depression is a risk factor for developing AD, or a prodromal sign of the disease^{2,5,9,12–14}. The weight of the evidence suggests that depression is likely a risk factor, though^{2,10,15}. This question remains partly due to the timing of studies that have been conducted in late-life, the variability in follow-up time, and also the fact that depression frequency and duration times are often not recorded².

Research has established that depression is associated with a greater risk for AD. Many studies have concluded that depression doubles an individual's risk of developing dementia, particularly AD^{7,9,10,16,17}. Other studies on depression and AD have shown that those who develop depression are 1.5 times more likely to develop AD compared to those who

are not depressed⁹. The evidence is not yet conclusive as to if early or late-onset depression might be a greater risk factor, but the severity of late-life depression has been found to be an important risk factor for dementia^{2,7}. Some studies have shown that depression in earlier life is more closely associated with vascular dementia, and depression in later life is a greater risk for developing AD¹⁸.

APOE $\epsilon 4$ status has been linked to higher rates of depression and is a definitive risk factor for AD^{5,19}. A study completed in India found that those with APOE $\epsilon 4$ had a 4.7 times higher risk of developing depression in old age²⁰. Populations in Sweden with the APOE $\epsilon 4$ gene also had a higher risk of developing depression. Furthermore, APOE $\epsilon 4$ is associated with more severe depressive symptoms⁴. Post-mortem studies have reported greater hippocampal amyloid plaque and neurofibrillary tangle pathology in AD patients with a history of depression than those without²¹.

While the specific pathway, or pathways, linking depression and AD have not been defined yet, many mechanisms have been hypothesized. Depression may lead to an increase in amyloid plaques through the depression-associated stress response. This response ultimately results in an increase in β amyloid production²². Chronic inflammation also plays a significant role in the pathophysiology of AD²³ and is seen in both depression and AD²⁴. It is hypothesized that stress leads to chronic inflammation in depressed persons. Neuroendocrine changes comparable to those found in chronic stress have also been found in depression and AD models¹⁰. Additionally, pro-inflammatory cytokines have been shown to interfere with serotonin metabolism, leading to a reduction in synaptic plasticity and hippocampal neurogenesis^{22,23}. Increased cortisol production can also lead to atrophy in the hippocampus and cognitive deficit²⁵. Interleukin-6 (IL-6), C-reactive protein, and tumor necrosis factor are all increased in depression and may be risk factors for dementia²⁶. Brain-derived neurotrophic factor (BDNF), often associated with synaptic plasticity, is decreased in depression and AD²⁷. Furthermore, MRI studies have found that hippocampal atrophy occurs in cases of depression, suggestive of AD pathology²⁸. Lastly, many lifestyle factors associated with depression are also known risk factors for AD, including poor diet, lack of physical activity, and low social engagement^{1,9}.

Of the studies conducted on depression and AD, this author could not find one that examined the link between depression, AD, APOE, and depression-inducing-drugs (DIDs). Drug-induced depression, also referred to as substance-induced mood disorder in the literature, is a well-known side effect of many medications. The first notion of a "depressogenic" drug was documented in 1954, referring to long periods of treatment with the antihypertensive drug reserpine²⁹.

Older populations have a greater risk of exposure to DIDs, as they are more likely to be on multiple medications^{8,30–32}. It has been found that the use of multiple medications increases the risk of simultaneous depression and that older age is significantly associated with the use of DIDs⁸.

The most common DIDs include narcotics, benzodiazepines, anticholinergic medications, antidepressants, sedatives, beta-blockers, calcium channel blockers, and oral contraceptives^{8,30,33}. The mechanisms for a few depressogenic drugs have been studied, and their additive risk factor for AD cannot be ruled out. In one longitudinal study, seven out of 15 individuals who developed AD had been taking antidepressants⁵.

Possible mechanisms for DIDs have been proposed³⁴. These mechanisms include inhibiting calcium-dependent neurotransmitter release by blocking the inflow of calcium into cells³⁵, decreased serotonin³⁶, reduction in G-protein-coupled catecholaminergic or cholinergic receptors³⁷, decreased levels of dopamine³⁸, and displacing nicotine from acetylcholine receptors³⁸. Because of the wide range of drugs that can cause this side effect, there is “no known reason to presume that all drugs produce depression via a common pathophysiological mechanism”³⁴.

Drug-induced depression is more likely to occur in those who have a higher risk factor for depressive disorder, as may be the case for individuals with the APOE ϵ 4 allele. For those already predisposed to depression, such as carriers of APOE ϵ 4, DIDs might have an amplified effect, leading to more frequent occurrences of depression.

Here, the author examined the prevalence of DIDs in elderly non-symptomatic and symptomatic AD patients to find how many DIDs the population was taking, the prevalence of depression, and whether APOE ϵ 4 status has any effect on depression levels with concurrent DIDs.

Methods

Bioinformatics platform

The data presented here is from uMETHOD Health's (uMH) database of patients. uMH has created a precision-medicine platform to create personalized treatment plans for patients with and at risk of dementia and AD³⁹. All individuals self-selected to follow their treatment plan. The treatment program was recommended to them by their physician, or they found uMH online and chose to purchase the personalized evaluation and treatment.

uMH's platform identifies and addresses active issues and creates repeatable and practical treatment plans for use in doctors' practices.

The bioinformatics platform's internal software is written in the Python language. It interfaces to an external portal, used by the medical and coaching teams to gather input, and returns reports written in PHP and Java. External medical databases support internal rules-processing algorithms. These are sourced from bodies such as the National Institutes of Health (NIH), Food and Drug Administration (FDA), pharmaceutical trade groups, and consortia focused on topics such as genetics or allergies.

Natural language processing (NLP) techniques are used throughout the input steps, particularly for precise identification of lab tests, medications, drug indications, and comorbidities. A range of NLP techniques are employed to normalize input data. The algorithms that implement this information platform go through a consistent set of steps each time they load a person's input to generate a new set of reports. These steps are rules-based, so the logic and evidence sources can be tracked (and evaluated).

The platform was used as a source of data only and was not used for data analysis in this study.

Dataset

The data set consists of all the patients in uMH's database who were 65 or older.

The inputs to uMH's data-analytics engine comprise genomics, bio-specimen measurements, medical histories, medications, allergies, comorbidities, lifestyle data, and cognitive evaluations. Data was collected from physicians, patients, and caregivers from annual wellness visits and through uMH's patient forms. Forms were completed online via uMH's secure portal or in paper format, depending on the individual's computer skills and access. Physicians were instructed to follow a set of inclusion and exclusion criteria from Keine *et al.* 2018³⁹ before enrolling patients.

Each patient was evaluated by a physician to determine if they were symptomatic for AD following standard of care guidelines⁴⁰. This evaluation included administering a baseline cognitive test to determine patients' cognitive status at the time of enrollment. The physician chose to administer either the Self-Administered Gerocognitive Exam (SAGE) or the Montreal Cognitive Assessment. Cognitive impairment was determined following each tests' specific guidelines^{41,42}. Tests were scored at the physician's office by trained personnel, and completed tests were either uploaded to uMH's secure portal or were sent to uMH by the physician's office to be entered into the database. The physician then used the findings to qualify the patient as symptomatic or non-symptomatic in uMH's database.

Genomic data was obtained through consumer-focused companies such as 23andMe or Ancestry.com. Interested patients purchased a genomic kit through the company of their choice and followed the procedures outlined by the genomic testing company. Raw datasets were accessed by the patient directly from the genomic company's website and uploaded to uMH's secure portal. As this was an optional step, many people chose to complete their analysis without genomic information. Therefore, APOE ϵ 4 status is only known for a subset of the population presented here.

Depressive symptoms were determined through patients' self-reporting, the Short Form Geriatric Depression Scale (SF-GDS)

at the physician's office⁴³, prior physician diagnosis as indicated by the patient's medical history, or a prescription for antidepressant medication.

DIDs were identified from Qato *et al.* Table 2⁸. The DIDs listed here were coded into uMH's bioinformatics platform so that each patient's medication list from uMH's database was checked against this published list by the platform's algorithms.

Study design

The data was analyzed using statistical methods to examine the prevalence of DIDs and depression in an elderly population currently at risk of or diagnosed with AD. The frequency of DIDs, antidepressant medications, and depression was analyzed against gender, cognitive impairment levels, depression symptoms, and current medications. This information was then subsequently compared to APOE status to investigate if a possible relationship exists between the APOE ε4 allele and depression levels, with or without DIDs.

Statistical analysis

All statistical analyses were performed using SAS University Edition. Power calculations for independent, two-sided t-tests were completed to compare population means. Either pooled or Satterthwaite P values were used based on equality of variance testing. Chi-square tests were completed for categorical data. Means, standard deviations, and frequencies were established using SAS. Significance was determined using a 95% confidence interval.

Ethical statement

Following the guidelines put forth in the 21st Century Cures Act⁴⁴, Clinical Decision Support Software (CDSS) is not regulated by the FDA, and uMH's treatment protocol does not include any investigational drugs. Because of this, the platform was taken straight to market and did not need approval by an ethics committee or board.

uMH's algorithm platform automatically assigns every participant a random eight-character ID when they are first entered into the system to de-identify their information. All data was collected under their randomly assigned ID, and the investigators here only had access to this de-identified information.

The data presented here is an analysis of data already gathered from patients; no experiments were performed on humans. Each participant self-selected to participate under the guidance of their individual physician. No patients were recruited by uMETHOD Health. All patients gave consent upon initial data collection and were informed that their de-identified information would be used for future research purposes. For patients who presented with cognitive decline, their caregiver or power of attorney was also informed of all data collection and gave consent to use de-identified data for future research.

Results

Utilizing uMH's data set, 292 individuals were analyzed for this paper (Table 1). A total of 189 people chose to provide genomic data. Of these 189, 111 have at least one copy of the APOE ε4 allele (Table 1). Those with the APOE ε4 allele are referred to as ε4 and those without are referred to as nε4. This population took an average of 11.51 (SD 8.86) medications per person, and 1.16 (SD 1.27) DIDs per person. The maximum number of DIDs seen for one person was five (Table 1).

Depression

36.21% of the population had depressive symptoms (Table 1). Individuals with depression were significantly more likely to be taking at least one DID (71.15% vs 28.85%, P value 0.005) (Table 2 and Figure 1). Those with ε4 had a significantly higher rate of depression than nε4s (69.12% vs 30.88%, P value 0.03) (Table 2). Females were also more likely to be depressed than males (65.71% vs 34.29%, P value 0.005) (Figure 2). The same held true when APOE ε4 status was

Table 1. Population overview.

Variable	Mean	Std Dev	Minimum	Maximum	N	% Population
Age (years)	75.62	7.27	65.18	102.46	292	100
Education (years)	16.13	3.48	5	24	194	-
BMI	26.34	5.03	17.4	45.9	263	-
Medications	11.51	8.86	0	67	284	97.48
DIDs	1.16	1.27	0	5	172	60.56
Antidepressants	0.43	0.76	0	4	84	29.58
Male	-	-	-	-	132	45.21
Female	-	-	-	-	160	54.79
Depressed	-	-	-	-	105	36.21
Cognitive impairment	-	-	-	-	171	75.33
APOE ε4 Male	-	-	-	-	55	56.12
APOE ε4 Female	-	-	-	-	56	61.54

BMI, body mass index; DIDs, depression-inducing drugs.

Table 2. Depression, gender, APOE, cognition, and drug comparison.

	Gender				APOE status			DIDs			Cognitive status		
	Female	Male	χ^2 P value	T-test P value	$\epsilon 4$	χ^2 P value	T-test P value	Taking DID	χ^2 P value	T-test P value	Cognitively impaired	χ^2 P value	T-test P value
Depression	65.71%	34.29%	0.005	-	69.12%	0.031	-	71.15%	0.005	-	78.48%	0.421	-
Depression and $\epsilon 4$	68.09%	31.91%	0.002	-	-	-	-	51.06%	0.721	-	74.42%	0.718	-
Antidepressants	67.86%	32.14%	0.005	0.029	70.00%	0.084	0.613	77.38%	0.0002	<.0001	80.00%	0.316	0.036
DIDs	59.30%	40.70%	0.067	0.045	55.10%	0.167	0.147	-	-	-	57.49%	0.394	0.136
$\epsilon 4$	50.45%	49.55%	0.450	-	-	-	-	49.09%	0.167	-	72.55%	0.038	-
Cognitive impairment	54.39%	45.61%	0.301	-	68.52%	0.038	-	57.49%	0.394	0.136	-	-	-

DIDs, depression-inducing drugs.

Figure 1. Depressed on DID vs no DID. Proportion of depressed patients taking a DID versus depressed patients not on DID. DID, depression-inducing drug. **Figure 2. Gender analysis.** Analysis of the percentage of each gender with depression, depression and APOE $\epsilon 4$, taking antidepressant medication, taking a depression-inducing drug (DID), possessing the APOE $\epsilon 4$ allele, and measurable cognitive impairment.

considered with gender (68.09% vs 31.91%, P value 0.002) (Table 2).

DIDs

60.56% of the total population was taking at least one DID (Table 1). Females were more likely to be taking a greater number of concurrent DIDs than males (1.29 [SD 1.32] vs 0.99 [SD 1.19], P value 0.045) (Table 2 and Table 3 and Figure 2). Those taking a DID were more likely to be taking a higher number of antidepressants (0.58 [SD 0.88] vs 0.2 [SD 0.46], P value <0.0001) (Table 2 and Table 3).

Antidepressants

29.58% of the overall population was taking at least one antidepressant medication (Table 1). Those taking an antidepressant were more likely to be taking concurrent DIDs (77.38% vs 22.62%, P value 0.0002) (Table 2). Gender was also a significant factor for antidepressants. Females were more likely to be on at least one antidepressant (67.86% vs 32.14%, P value 0.005) (Figure 2), as well as taking a greater number of concurrent antidepressants (0.52 [SD 0.80] vs 0.32 [SD 0.71], P value 0.029) (Table 2 and Table 3).

A higher, though not statistically significant, number of people taking antidepressants were more likely to have $\epsilon 4$ (70% vs 30%, P value 0.084) (Table 2).

Cognitive impairment

75.33% of this population had measurable cognitive impairment (Table 1). Those who were impaired took a higher number

of concurrent antidepressant medications (0.46 [SD 0.83] vs 0.25 [SD 0.52], P value 0.036) (Table 2 and Table 3). There was also a higher percentage of cognitively impaired individuals taking antidepressants, but the number did not reach significance (80% vs 20%, P value 0.316). A higher percentage of people with cognitive impairment were also taking DIDs (57.49% vs 42.51%, P value 0.394), but again the number did not reach significance (Table 2).

Discussion

DIDs are a substantial clinical, medical, and public health problem³⁴ that has yet to be addressed in older populations. DID consideration is especially important in populations with an increased risk or a current diagnosis of AD. Prescriptions for elderly patients, especially those with a family history of AD or who currently have symptoms of cognitive decline, should be closely monitored and should avoid taking DIDs whenever possible.

The results of this work support that $\epsilon 4$ populations are at a greater risk of depression. Whether depression is a prodromal symptom or a risk factor for AD cannot be concluded from this data, but many other studies provide compelling evidence that depression may contribute to a person's risk of developing AD. If depression is a precursor to AD, then DIDs may accelerate the clinical presentation of AD. It is worth further study to see if those who possess the $\epsilon 4$ allele should avoid drugs likely to cause depression symptoms, as they may be predisposed to develop depression. Further research into the possible mechanisms of DIDs is also warranted and

Table 3. Drug analysis.

Drug		Mean	Std Dev	Minimum	Maximum	Count on medication	% Population
Antidepressants	Female	0.52	0.80	0	4	57	67.86
	Male	0.32	0.71	0	3	27	32.14
Antidepressant	No cognitive impairment	0.25	0.52	0	2	12	20.00
	Cognitive impairment	0.46	0.83	0	4	48	80.00
Antidepressant	nE4	0.35	0.82	0	4	15	30.00
	E4	0.41	0.65	0	2	35	70.00
Antidepressant	No DID	0.20	0.46	0	2	19	22.62
	DID	0.58	0.88	0	4	65	77.38
DIDs	Female	1.29	1.32	0	5	102	59.30
	Male	0.99	1.19	0	5	70	40.70
DID	No cognitive impairment	0.82	1.09	0	5	28	22.58
	Cognitive impairment	1.11	1.29	0	5	96	77.42
DID	nE4	1.01	1.08	0	5	44	44.90
	E4	0.78	1.04	0	5	54	55.10
DID	Not depressed	0.97	1.14	0	5	97	56.73
	Depressed	1.49	1.42	0	5	74	43.27

DIDs, depression-inducing drugs.

could possibly help further elucidate the correlation between depression and the development of AD.

This work also showed that DIDs are abundant in elderly individuals' medication regimes. Re-evaluation of medications that have been documented to cause depression could potentially lead to better cognitive function for many patients. This may be especially beneficial to the $\epsilon 4$ population. Further research may improve guidelines for prescribing DIDs to elderly patients, and additional specifications may be needed for those with the $\epsilon 4$ allele.

Females appear to be at an even greater risk for DIDs as this study found they may already be pre-disposed to depression, with the risk increasing with the $\epsilon 4$ gene, and are more likely to be taking DIDs and taking a higher number.

Further research is warranted to see if patients with different levels of cognitive impairment respond differently to DIDs, or if there are other contributors to developing depression as a side effect. Other factors such as age, body mass index, and comorbidities could also be explored to see if they impact patients' risk of developing DID.

With the rising numbers of elderly in the US, along with concurrent use of multiple prescription drugs, DID burden on cognitive health continues to grow. 30% of older adults in the United States take five or more medications daily⁴⁵, known as polypharmacy. Each additional drug increases a patient's risk of experiencing adverse effects, including depression and cognitive impairment.

CDSS provides a reliable and reproducible method to help with polypharmacy and DIDs. CDSS is software that is created to provide decision support for the diagnosis, treatment, prevention, cure, or mitigation of diseases or other conditions⁴⁴. The goal of CDSS is to provide clinicians with actionable recommendations to improve clinical decision making^{46,47}. One considerable advantage of CDSS is its inherent ability to process immense amounts of data quickly. This makes CDSS ideal for dealing with complicated medication regimes.

Machine-learning algorithms, one element of CDSS, can be equipped to help physicians and patients better curate their medications to prevent adverse events, unwanted side effects, and even duplicated prescriptions. It's estimated that 25% of people aged 65–69 take at least five prescriptions, and it is not uncommon for people to take 20 or more drugs⁴⁸. One individual in this dataset was on a total of 67 medications. The considerable number of patients with polypharmacy and an average of 32 new drugs approved by the FDA each year make this an insurmountable task for a physician to take on by themselves⁴⁹.

CDSS can quickly review a patient's medication list, no matter how large, matching it to current guidelines to provide physicians with reproducible guidance. This guidance could include recommendations for deprescribing medications that are therapeutically repetitive, medications that interact with other

drugs, and medications that interact or have diminished therapeutic benefit due to an individual's genetics. CDSS can also alert physicians to medications such as DIDs and anticholinergic drugs that have been shown to cause cognitive burden for elderly patients. CDSS also has the ability to suggest formulary alternatives to reduce the amount of DIDs in a medication list.

CDSS has the potential to support pharmacogenomics. Pharmacogenomics is the study of identifying genomic variants that affect drug efficacy and pharmacokinetics (PK) or pharmacodynamics (PD)⁵⁰. There are many examples of medications that are effective or ineffective for patients based on their genome, including antidepressants. As of 2015, 20 genetic variations have been found that can affect around 80 medications⁵⁰. In fact, one gene can affect multiple medications. Many of uMH's clients choose to get their genome sequenced to find out more about their genetic risk and protection against AD. This same data can also be used to help select the most beneficial medications for each person.

uMH's bioinformatics platform currently mines publicly available databases to check for drug-gene interactions (DGIs). The platform analyzes more than 2,000 single nucleotide polymorphism (SNPs) per individual, some of which pertain to DGIs, others are used to quantify the genetic risk of AD as well as other genetic diseases.

DGI information is drawn from three sources of pharmacogenomic information: the Clinical Pharmacogenetics Implementation Consortium (CPIC) effort⁵¹, DrugBank^{52,53}, and SNPedia's SNP and genoset compilations^{54,55}. DGIs are looked at in two categories: genetics that influence how enzymes metabolize each drug, and relationships between specific genes and drugs. Each medication a person is currently taking is compared against a table of genes that affect it, and these genes are, in turn, compared to those in the person's genome.

Approximately half of the people placed on an antidepressant medication do not show signs of improvement and over half will experience an adverse side effect. This is partly due to each person's genetic makeup and its impact on the PK and PD of the medication⁵⁶. Many pharmacogenomic studies have been conducted on antidepressant medications and found that their efficacy is highly correlated with SNP variations. Metabolizing enzymes such as P450 and the *CYP2D6* polymorphism have both been found to have an effect on the drug plasma levels of antidepressant medications⁵⁷.

Precision-medicine platforms, like uMH's CDSS, offer the opportunity to improve the fitting of a drug to a patient with less trial and error, based on their genetics. This would allow for patients to be placed on the most effective medication as soon as possible, potentially speeding up recovery time from depressive symptoms.

CDSS could also be made more effective if linked to systems pharmacology models. These models have been developed to help predict *in vivo* drug effects in biological networks^{58,59}. This

approach seeks to look at the whole, instead of the more traditional single transduction pathway of drug administration and response. Drugs often have off-target or secondary effects that can be hard to predict as multiple systems can be involved and must be accounted for. Patients' responses to drugs are also inherently variable due to their unique genome, environment, disease state, and the high prevalence of polypharmacy^{32,58}.

A systems biology analysis could be useful in further defining the mechanisms behind DIDs. This information could then further inform future research into potentially lessening the depressive effects of these drugs, and also inform research into whether depression is a true risk factor for AD or a prodromal symptom.

Many older adults who experience late-life depression never fully recover from their depression-induced cognitive impairment, even after successful treatment of the depression. All these observations magnify the urgent need to provide better vigilance when prescribing medications for the elderly.

A more technology-friendly view is needed when it comes to managing complex medication regimes, especially when medications that can affect patients' cognitive abilities are involved (as evidenced by the lack of publications on DIDs and the AD population).

The findings presented here support numerous previous publications indicating a relationship between depression and cognitive decline. While our observational data can only provide conjecture and find correlations, it is clearly worth closely monitoring DIDs in elderly populations. It is of even more importance when a patient may already be at increased risk of

AD. There is a better path forward for patients with precision medicine and CDSS.

Data availability

The data that support the findings of this study are available from uMETHOD Health but restrictions apply to the availability of these data, which are proprietary company information, and so are not publicly available. Data are, however, available with permission of uMETHOD Health. Requests will be granted on a case-by-case basis to researchers affiliated with an accredited institution following the submission of an ethically approved and relevant research proposal. Readers and reviewers can request access to the dataset used in this manuscript by sending a request to info@umethod.com. The [National Alzheimer's Coordinating Center \(NACC\)](#) database is a publicly available dataset that is representative of the dataset analyzed in this study and can be used to apply the methodology described in this manuscript.

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Authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

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Dr. John R. Cirrito confirms that the author has an appropriate level of expertise to conduct this research and confirms that the submission is of an acceptable scientific standard. Dr. John R. Cirrito declares they have no competing interests. Affiliation: Department of Neurology, Washington University, St. Louis, USA.

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Marina Sagud

Department for Psychiatry and Psychological Medicine, School of Medicine, University Hospital Center Zagreb, Zagreb, Croatia

This study has used data from the uMH's data set, in order to establish the association between the presence of at least one APOE $\epsilon 4$ allele and depression-inducing drugs, and symptoms of depression (widely defined), in individuals aged 65 and older. The results highlight the connection of both APOE $\epsilon 4$ alleles and the intake of depression-inducing drugs, with symptoms of depression in elderly population. The study needs revision, as provided below.

Introduction

- Instead of, "the APOE $\epsilon 4$ gene", which is mentioned several times in the text, I think it is more accurate to say: "the APOE ϵ gene".
- Please, provide a short description about APOE ϵ gene, and its three major alleles (epsilon 2, epsilon 3, and epsilon 4), prior to APOE ϵ gene subsection.
- The notion that antidepressants are among the depression-inducing-drugs appears counter-intuitive. Please, explain further.

Methods

- Dataset-Depressive symptoms were determined through patients' self-reporting, the Short Form Geriatric Depression Scale (SF-GDS), prior physician diagnosis as indicated by the patient's medical history, or a prescription for antidepressant medication - antidepressants are also prescribed for other disorders, such as PTSD, anxiety and chronic pain disorders. How can you differentiate those patients?
- Please, provide the short description of the SF-GDS, the Self-Administered Gerocognitive Exam (SAGE) and the Montreal Cognitive Assessment scale. What were the cut-off values for the depression from the SF-GDS, and for the cognitive impairment from the cognitive scales?

Results

- Was the power analysis conducted to calculate the minimal sample size?

- Participants with at least APOE $\epsilon 4$ allele were referred to as $\epsilon 4$, but the number of APOE $\epsilon 4$ alleles was not analyzed. Because there is difference in the AD risk between the carriers if one or two APOE $\epsilon 4$ alleles, this should also be mentioned in the Limitations.
- "Those with $\epsilon 4$ ", or " $\epsilon 4$ populations" should be replaced with " $\epsilon 4$ allele carriers".

Discussion

- I propose to organize the discussion in several subsections.
- The term "depression" measured in this study refers to both current (as measured by the SF-GDS scale) or past (from the patient's medical history). Please, emphasize in the text that this study addressed "life-time", rather than current depression.
- 29.58% of the overall population was taking at least one antidepressant medication-please, compare this data from other authors in the similar samples.
- The findings presented here support numerous previous publications indicating a relationship between depression and cognitive decline-please, provide references.
- Many older adults who experience late-life depression never fully recover from their depression-induced cognitive impairment, even after successful treatment of the depression -please, provide references.
- Please, mention study limitations.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Psychopharmacology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 20 August 2020

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Carola G. Schipke

Predemtec AG, Gossau, Switzerland

This manuscript aims to analyse the frequency of use of depression-inducing drugs in Alzheimer's disease (AD) and APOE ε4 carriers. The author collected datasets from a commercial platform (uMETHOD health) that advertises that it combines big data, medical research, and advanced algorithms to enable personalized care.

The manuscript picks up an important and highly relevant question but needs some major revisions since the way the data is presented, it does not allow for all the conclusions made.

In the introduction, the only reference given regarding Alzheimer's disease in any aspect is a publication on facts by the Alzheimer's Association, no original research work is cited. In the 2nd paragraph of the introduction, the author writes that 35.6 million people worldwide have AD. This is wrong, the paper that is cited says that "...Currently, there are 35.6 million individuals with dementia worldwide..". It is crucial to understand and to state that dementia is not synonymous with AD. Also, no citation is given for the number of AD patients in the US, the number stated in the manuscript is not in reference 2 (that is given for the complete sentence). The 1st sentence in the 3rd paragraph of the introduction that starts with the words "Research now suggests" gives a reference that is 20 years old. References need to be updated.

In the methods section (and table 1) it is not completely clear, why the overall number of 292 patients is given, but only for 284 information on medication is available. Apparently, percentages in table 1 refer to 284, which is logical. Also, the author states that patients were evaluated to determine if they had AD, but no numbers or results are given, not even the methods used are stated. At least the type of examinations that were used to exclude other forms of dementia should be listed.

A major drawback is the lack of information on the severity of cognitive impairment. This can largely influence depressive symptoms - and measures for depressive symptoms, the author needs to state the values (total and z-scores) for the mentioned cognitive test for the cohort. It should be discussed if patients presenting with moderate dementia or worse should be included at all into this study.

Results:

Table 1 states that 84 patients or 29.58% of the population take antidepressants. Figure 2 states that 67.86% of the females and 32.14% of the males take antidepressant. How come the overall percentage is lower than the percentages in males and females? Please clarify.

For Figure 2: How many patients do take DIDs because of a diagnosed depression? This number should be looked at and should be taken into consideration for all analyses, since depressive symptoms only improve slowly, and since antidepressant medication is counted as a DID, it is somehow clear - and misleading with regard to the main point of the manuscript - that people diagnosed with depression take antidepressant drugs.

Discussion:

The discussion picks up important points regarding the interrelations of AD and depression. What is puzzling me is the extreme focus on the software and the platform, paragraphs 7-12 discusses the software/platform. While topics discussed in these paragraphs are generally important, this is like a commercial for me and in my opinion, large parts have nothing to do with the scientific facts reported in the paper.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: CGS is an employee of Predemtec AG.

Reviewer Expertise: biochemistry, molecular neuroscience, biomarkers, Alzheimer's disease, diagnosis of Alzheimer's disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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