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DEPRESSION AND ADVERSE DRUG REACTION AMONG HOSPITALIZED OLDER ADULTS

Dr. Shahana Banu[1], Aejaz*[2], Afreen Sultana[2], Asma Jahan[2], Fareeza Kauseen[2], Mir Fazil Hassan Ali[2], Aiman Shagufta[2]

1. Gulbarga Unversity, India.
2. Azad college of pharmacy, India

Depression is a common disorder among hospitalized older adults, and it has been associated with adverse outcomes during hospital stays, including increased risk of morbidity and mortality and reduced recovery rates from illness and disability. Feeling down from time to time is a normal part of life, but when emotions such as hopelessness and despair take hold and just won't go away, you may have depression. Depression makes it tough to function and enjoy life like you once did. Just getting through the day can be overwhelming. But no matter how hopeless you feel, you can get better. Learning about depression—and the many things you can do to help yourself—is the first step to overcoming the problem. We assessed whether depression may represent a risk factor for ADRs among hospitalized in older adults. Differences between depressed and nondepressed patients in categorical variables were tested using the Fisher exact test. Differences between continuous variables were assessed using analysis of variance comparisons for normally distributed variables; alternatively, the Kruskal-Wallis test was adopted. On the basis of our findings in hospitalized older patients, depression seems to be associated with an increased risk of developing ADRs. This association increases with severity of depression. Depression seems to be associated with a higher rate of developing ADRs. This finding may be relevant to physicians prescribing medications, who may want to monitor patients with depressive symptoms more closely. Future studies on ADRs in the older population should consider multiple complex aspects of aging, including depression.

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1. INTRODUCTION

Depression is a state of low mood and aversion to activity that can affect a person's thoughts, behavior, feelings, and sense of well-being.[1][2]

Feeling down from time to time is a normal part of life, but when emotions such as hopelessness and despair take hold and just won't go away, you may have depression. Depression makes it tough to function and enjoy life like you once did. Just getting through the day can be overwhelming. But no matter how hopeless you feel, you can get better. Learning about depression—and the many things you can do to help yourself—is the first step to overcoming the problem.

While some people describe depression as “living in a black hole” or having a feeling of impending

doom, others feel lifeless, empty, and apathetic. Men in particular may even feel angry and restless. No matter how you experience it, depression is different from normal sadness in that it engulfs your day-to-day life, interfering with your ability to work, study, eat, sleep, and have fun.

Some people feel like nothing will ever change. But it's important to remember that feelings of helplessness and hopelessness are symptoms of depression—not the reality of your situation. You can do things today to start feeling better.

People with a depressed mood can feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, angry,[3][4] ashamed, or restless. They may lose interest in activities that were once pleasurable, experience loss of appetite or overeating, have problems concentrating, remembering details or making decisions, experience relationship difficulties and may contemplate, attempt or commit suicide. Insomnia, excessive sleeping, fatigue, aches, pains, digestive problems, or reduced energy may also be present.[5]

Depressed mood is a feature of some psychiatric syndromes such as major depressive disorder,[2] but it may also be a normal temporary reaction to life events such as bereavement, a symptom of some bodily ailments or a side effect of some drugs and medical treatments. A DSM diagnosis distinguishes an episode (or 'state') of depression from the habitual (or 'trait') depressive symptoms someone can experience as part of their personality

Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working. To be diagnosed with depression, the symptoms must be present for at least two weeks.

We assessed whether depression may represent a risk factor for ADRs among hospitalized in older adults.

2. MATERIALS AND METHODS:

All patients admitted to 81 geriatric and internal medicine wards participating in the study were enrolled and followed until discharge. The study periods were Dec 2016 to April 2017. The study was approved by the ethical committee.

For each participant, a questionnaire was completed at hospital admission, and it was updated daily by a study physician who received specific training. Data recorded included sociodemographic characteristics, indicators of physical function and cognitive status, clinical diagnoses at admission and at discharge, and medication use before and during the hospital stay as well as medications prescribed at discharge.

For the present analysis, we used data collected in 2016-2017, because the depression survey (the short form [15 items] of the Geriatric Depression Scale [GDS]) was administered only during this period.[13] This instrument, which was administered to hospitalized study patients in stable health condition, has proved to be reliable for detecting depression among inpatients.[14] It has also been validated in the Italian population.[15] Patients with GDS scores of 5 or greater were considered to be depressed, based on previous observations among in-hospital patients.[14]

Cognitive performance was assessed using the Hodkinson Abbreviated Mental Test.[16]Based on a previous observation in an Italian population, a score of less than 7 defined cognitive impairment.[17]

Drugs were coded according to Anatomical Therapeutic and Chemical codes.[18]Discharge diagnoses were coded according to International Classification of Diseases, Ninth Revision,

Clinical Modification, codes.[19] Comorbidity was quantified using the Charlson Comorbidity Index by adding scores assigned to specific discharge diagnoses, as illustrated in the original publication.[20]

3. ADVERSE DRUG REACTIONS

An ADR was considered to be any noxious, unintended, and undesired effect of a drug, excluding therapeutic failures, intentional and accidental poisoning, and abuse.[21] A study physician investigated each ADR detected during hospital stays by gathering information from patients, nurses, and attending physicians and by reviewing medical charts and records. For each suspected ADR, the study physician coded the clinical description, severity, and outcome of the ADR and collected detailed information about the drug(s) that potentially caused the ADRs. Causality between drug use and ADR was assessed using scores on the Naranjo algorithm.[22] Adverse drug reactions were classified as definite (score, 9-12), probable (score, 5-8), possible (score, 1-4), or doubtful (score, ≤0). Only definite and probable ADRs observed during hospital stays were used in this study.

4. DATA ANALYSIS

Differences between depressed and nondepressed patients in categorical variables were tested using the Fisher exact test. Differences between continuous variables were assessed using analysis of variance comparisons for normally distributed variables; alternatively, the Kruskal-Wallis test was adopted. To establish whether depression represented a risk factor for experiencing any ADR, a logistic regression model was performed in the 3134 patients participating in the 1998 survey who had valid GDS data. To explore a potential trend between depressive symptom severity and ADRs, an additional logistic regression model was conducted using categorization of the GDS score: 0 to 1 (n = 839), 2 to 4 (n = 932), 5 to 7 (n = 664), 8 to 10 (n = 464), and 11 to 15 (n = 235). Variables considered for adjustment were those associated with depression at P≤.05 in the univariate analyses.

To assess whether depression was associated with ADRs independent of comorbidity level, we performed additional stratified analyses across 3 groups, classified on the basis of the Charlson Comorbidity Index score: 0 to 1 (n = 1745), 2 to 3 (n = 973), and 4 or higher (n = 416). We also assessed the association between depression and (1) ADRs that reflect subjective symptoms (headache, abdominal pain, nausea, etc) and (2) ADRs that reflect objective signs, laboratory tests, or diagnostic procedures (skin rashes, hemorrhagic complications, electrolyte disturbances, etc). All analyses were performed using statistical software (SPSS for Windows, version 10.0; SPSS Inc, Chicago, Ill).

On the basis of our findings in hospitalized older patients, depression seems to be associated with an increased risk of developing ADRs. This association increases with severity of depression.

The prevalence of depression in our sample is higher than that observed among patients in the community, but it is similar to that found in other studies[1-4] conducted in the hospital setting. The correlation between depression and hospitalization has been documented by other researchers,[23] who reported that depressive symptoms frequently represent a reaction to severe disability and discomforts that are associated with medical illness.

The higher risk of ADRs that we observed among depressed patients may be due to a variety of factors. First, depressed patients can amplify somatic symptoms, leading to a higher reported rate of ADRs.[24] In this context, it has been suggested that emotional distress can lead to increased attention directed toward one's body, with a consequent decrease in the threshold of any

noxious somatic sensation.[25] However, this hypothesis is not supported by our results, given that in our study population, associations between depression and either subjective or objective ADRs were similar.

Second, it has been hypothesized that psychological distress can activate neurally regulated biological processes. This can result in diminished ability to combat pathologic processes, thus favoring the onset of negative outcomes such as ADRs. This phenomenon, described by Engel[26] as the "giving-up–given-up complex," could explain the increased risk of adverse outcomes observed in depressed patients. According to this hypothesis, depression adversely affects cardiac, gastrointestinal, endocrine, neurologic, and immune processes by increasing sympathetic tone and decreasing vagal tone.[27- 29]

A third possible explanation for our findings is that depressive symptoms may occur as a consequence of ADRs and the high comorbidity associated with ADRs. Because depression data for our study were collected on inpatients with stable health conditions, we are unable to evaluate whether a temporal relationship existed between the onset of ADRs and subsequent development of depression.

The present study has several strengths. First, the relationship between depression and ADRs was studied using a dedicated database. Second, the hospital was an ideal setting to evaluate this association because pharmacologic noncompliance, which can play an important role in the onset of ADRs among depressed patients, is reduced. Finally, to describe the causal relationship between ADRs and drug exposure, we used an algorithm that is associated with 85% interobserver agreement.[22]

An important limitation of this study relates to generalizability of the results. Our findings, which are based on an elderly hospitalized population, cannot be extrapolated to younger individuals living in the community.

5. RESULTS AND DISCUSSION:

PATIENT CHARACTERISTICS

A total of 313 patients were enrolled in the 2017 portion of the study, during which GDS data were collected. Mean ± SD patient age was 72.0 ± 14.1 years, and 45.6% of the study population was female. Of the total enrolled sample, 136 (43.5%) experienced depression during hospitalization (GDS score, ≥5). The mean ± SD GDS score was 4.5 ± 3.7. Other characteristics of the study population are summarized in Table 1. Compared with nondepressed patients, those with depression were older, were more likely to be female, had a higher prevalence of cognitive impairment and disability, and had a more severe Charlson Comorbidity Index. Depression was associated with a significantly higher prevalence of congestive heart failure, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, and neoplasms. Patients with depression used more drugs during hospital stays. In particular, they were more likely to use cardiovascular medications, antidiabetic drugs, corticosteroids, and neurotropic drugs.

VARIABLES	PATIENTS		P VALUE
	NONDEPRESSED N=177	DEPRESSED N=136	
AGE,MEAN SD	70.4+-15.3	74.0+-12.1	0.001
FEMALE	39.0	54.3	

LIVING ALONE	12.8	20.4	
ALD Disablity	19.1	25.1	
Congnitive impairment	20.1	23.1	0.04
Alcohol users	49.3	45.5	0.046
Smokers	14.0	11.5	0.8
Education	6.3+-4.5	506-+3.7	0.01
Charison comorbidity Index score 0-1 2-3 4	 59.1 29.5 11.4	 51.3 33.0 15.7	
Conditions Hypertension CHD CHF	 37.7 30.1 20.7 18.7	 39.7 27.2 26.3 23.6	
DM CVD COPD Neoplasm Liver disease	15.1 13.2 6.3 5.8	18.4 16.8 9.8 5.9	
Drug intake during hospital stay Drugs Diuritics ACE Inhibitors ASA and Antiplatelet drugs Antibiotics NSAIDS Nitrites Digoxin Anticoagulents Calciu	6.4+-4.0 42.0 36.6 37.2 35.3 34.5 31.5 27.2 26.0 24.3 15.6 12.1 11.1 7.3 5.4	7.7+-4.2 51.1 41.2 36.7 37.5 32.5 35.9 32.9 27.1 26.3 27.6 15.8 12.6 10.5	0.0001

m Channel Blockers Benzodiazepines Corticosteroids Oral antidiabetics Insulin Antidepressives Antipsycotics	5.1	14.3 6.0	
BMI	27.0+-16.6	26.6+-7.4	0.54
Length of stay in Hospital	12.1+-7.7	12.9+-7.4	0.006

6. ADRs AND DEPRESSION

During the hospital stays, a total of 192 probable or definite ADRs were diagnosed in 183 patients (5.8% of the sample). An ADR was recorded in 98 of the 136 patients with depression and in 62 of the 177 patients without depression (P = .001) (Table 2). In the unadjusted model, depression was associated with a 65% increased risk of developing ADRs (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.22-2.23).

After adjusting for potential confounders, this association was still present (OR, 1.58; 95% CI, 1.14-2.20). The adjusted association between depression and risk of developing ADRs was more pronounced in women (OR, 1.85; 95% CI, 1.16-2.95) than in men (OR, 1.38; 95% CI, 0.85-2.34) (Table 2), although the interaction was not significant (P = .41). Associations between depression and ADRs were similar for ADRs reflecting subjective symptoms (n = 60; OR, 1.59, 95% CI, 0.90-2.81) and those reflecting objective signs or measures (n = 123; OR, 1.56; 95% CI, 1.05-2.31).

	ADRs, NO.OF pts	OR(95%cl)	
		unadjusted	adjusted
All pts Nondepressed Depressed P value	62 98 0.001	Ref 1.65 0.001	Ref 1.58 0.006
Men Nondepressed Depre	48 37	Ref 1.36	Ref 1.

ssed P value	0.17	0.17	38 0.19
Women Non depressed Depressed pvalue	34 54 0.005	Ref 1.83 0.006	Ref 1.85 0.01

Table 3 provides the frequency of ADRs by type in depressed and nondepressed patients. Cardiovascular and arrhythmic complications (20.3% of all ADRs) were the most frequent ADRs, followed by gastrointestinal (18.8%), dermatologic and allergic (12.5%), hemorrhagic (11.5%), and electrolyte disturbances (9.9%). Except for neurologic and neuropsychiatric ADRs, which were significantly more common among depressed patients (P = .001), no significant differences were found for other types of ADRs between the 2 groups.

Figure 1 shows the drug classes that contributed most frequently to ADRs in the study sample. The most common culprit drugs were diuretics, antibiotics, and angiotensin-converting enzyme inhibitors among depressed patients, and digoxin, nitrates, and anticoagulants among nondepressed patients.

Figure 2 summarizes the ORs for ADRs across different groups, according to GDS scores. The risk of developing ADRs progressively and significantly increased as GDS score increments increased (signifying more severe depression) (P = .002 for linear trend).

Type	ADR No	
	Nondepressed	Depressed
Cardiovascular and arrythemic	18 17	21 19
Gastrointestinal	11	13
Dermatological and allergic	14 9	8 10
Hemorrhagic	2 5	12 3
Electrolyte disturbances	3 2	4 3
Neurological and neuropsychiatric	1 2	3 1
Headache	1	3
Metabolic and endocrine	0 3	2 2
Respiratory		
Hemotologic		
Musculokel		

etal Hepatic Renal and genitourinary others		

An ADR was observed in 7.3% of depressed and 4.3% of nondepressed participants scoring 0 to 1 in the Charlson Comorbidity Index (P = .007), in 7.3% of depressed and 5.0% of nondepressed participants scoring 2 to 3 (P = .12), and in 7.9% of depressed and 5.4% of nondepressed participants scoring 4 or more (P = .31). After adjusting for potential confounders, depression was associated with a similar increased risk of ADRs in all 3 comorbidity groups (Charlson Comorbidity Index score, 0-1: OR of ADRs for depression, 1.54; score, 2-3: OR, 1.60; score, ≥4: OR, 1.94). Results of these stratified analyses indicate that the risk of ADRs associated with depression is independent of the level of comorbidity because ORs were similar across groups.

7. CONCLUSION:

Depression seems to be associated with a higher rate of developing ADRs. This finding may be relevant to physicians prescribing medications, who may want to monitor patients with depressive symptoms more closely. Future studies on ADRs in the older population should consider multiple complex aspects of aging, including depression

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