Early Antidepressant Resistance in Late-Onset Major Depressive Disorder: A Nationwide Population-Based Cohort Study

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ABSTRACT

Background: The association of treatment resistance with physical and psychiatric comorbidities remains unclear in elderly patients with late-onset major depressive disorder (MDD).

Methods: Participants were selected from the Taiwan National Health Insurance Research Database. We included patients aged ≥ 65 years with first-episode MDD (*ICD-9-CM* codes: 296.2X and 296.3X) between January 1, 2001, and December 31, 2010. All participants were followed for 1 year to investigate the incidence of treatment resistance. Treatment-resistant depression (TRD) was defined as unresponsiveness to at least 2 antidepressants, and treatment-resistant tendency (TRT) was defined as unresponsiveness to the first antidepressant. Physical comorbidities were assessed with the Charlson Comorbidity Index (CCI).

Results: 27,189 patients with late-onset MDD were included, among whom 16.6% had the diagnosis of anxiety disorders, 1.5% had alcohol use disorders, and 1.6% had substance use disorder. For physical comorbidities, only 16.6% of patients had a CCI score of 0. During the first year of treatment, 22.1% of patients met TRT criteria, and 1.6% developed TRD. Anxiety disorders (odds ratio: 2.06; 95% confidence interval [CI], 1.67–2.53), substance use disorders (2.11; 95% CI, 1.26–3.53), and higher CCI scores (1.06; 95% CI, 1.01–1.10) were significantly associated with TRD, while anxiety disorders (1.44; 95% CI, 1.34–1.55) and higher CCI scores (1.06; 95% CI, 1.05–1.08) were significantly associated with TRT.

Conclusions: Approximately one-fourth of elderly patients responded poorly to the first antidepressant treatment during the first year of late-onset MDD. Psychiatric comorbidities were more associated with the risk of early TRT than were physical comorbidities.

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Depression is a common mental disorder that is estimated to affect 322 million people worldwide.[1] It is also the major leading cause of 8 million suicide deaths per year. The World Health Organization ranks depression as the single largest contributor to global disability.[1] The prevalence rate of depression peaks in old age. It is estimated that 2%–5% of community-dwelling adults 65 years and older meet the diagnostic criteria of major depressive disorder (MDD).[2,3] Up to 10% of older adults seen in primary care[4] and 40%–50% of those in institutional and long-term care facilities have clinically significant depression.[5] In clinical practice, MDD has become one of the most common mental disorders in old age.

Over half of MDD arising in old age appears as a new condition rather than a recurrent one and is defined as late-onset MDD. A study reported that 52% of people in a geriatric mood disorders unit experienced their first episode of MDD at age 60 or older.[6] Another study examined elderly patients receiving home care for physical problems and reported that 71% of those with MDD were experiencing their first episode of depression.[7] Importantly, poor response to antidepressant treatment is more common in late-onset MDD than that in adult-onset MDD.[8,9] Besides, late-onset MDD often co-occurs with serious physical illnesses, and treatment resistance may worsen the outcomes of co-occurring medical disorders and increase non–suicide-related mortality.[10] When treatment resistance occurs, depression becomes a long-lasting condition, which may lead to functional disability and increase the risk for dementing disorders.[11,12]

To date, few studies have investigated early TRT and its association with physical or psychiatric comorbidities among patients with late-onset MDD. Previous studies

Clinical Points

- Although it is known that poor response to antidepressant treatment is more common in late-onset major depressive disorder (MDD) than in adult-onset MDD, the association between early treatment resistance and physical or psychiatric comorbidities in late-onset MDD remains unclear.
- Anxiety disorders and substance use disorders were associated with early treatment resistance in elderly patients with late-onset MDD during the first year of treatment.

addressing this issue usually had a small sample size.[13] Using a nationwide population database, we investigated the incidence of comorbid physical and psychiatric illnesses and treatment resistance to initial antidepressant treatment among patients with late-onset MDD. In the present study, treatment-resistant depression (TRD) was defined as unresponsiveness to at least 2 antidepressants, and treatment-resistant tendency (TRT) was defined as unresponsiveness to the first antidepressant in the patient's first year of treatment. We hypothesized that physical and psychiatric comorbidities were differently associated with early TRT in patients with late-onset MDD.

METHODS

Data Source

Taiwan's National Health Insurance (NHI) was implemented in 1995 and offers comprehensive medical care coverage to all Taiwanese residents (more than 23 million people).[14–16] The National Health Research Institute (NHRI) oversees the National Health Insurance Research Database (NHIRD), which is the entire insurance claims database and consists of health care data from > 99% of the entire Taiwan population. NHIRD was audited and released by NHRI for scientific and study purposes. Individual medical records included in the NHIRD are anonymized to protect patient privacy. Comprehensive information on insured individuals is included in the database, including demographic data, dates of clinical visits, disease diagnoses, and prescription. The diagnostic codes used were based on the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[17–20] This study was approved by the Taipei Veterans General Hospital Institutional Review Board (2018-07-016AC). All authors had access to the study data and reviewed and approved the final manuscript.

Inclusion Criteria for the Elderly With Major Depressive Disorder

We included elderly patients aged ≥ 65 years with first-episode MDD (*ICD-9-CM* codes: 296.2X and 296.3X) between January 1, 2001, and December 31, 2010. The time of MDD diagnosis was the enrollment time. All patients with MDD were followed for 1 year from the enrollment time to investigate the incidence of treatment resistance. We used a validated method to divide patients into 4 groups based on the antidepressant treatment regimens and treatment response to antidepressants during the first year of follow-up,[21] that is, easy to treat group 1, easy to treat group 2, intermediate difficulty to treat (IDTT) group, and difficult to treat (DTT) group. An adequate trial of antidepressant treatment was defined as using an antidepressant within its therapeutic dosage range (eg, fluoxetine ≥ 20 mg/d) for > 60 consecutive days. This criterion could reduce the possibility of misclassifying intolerability as nonresponse. Antidepressants included selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram), serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine, milnacipran), a norepinephrine-dopamine reuptake inhibitor (bupropion), and mirtazapine (see Supplementary Table 1 for dosage ranges). Prescription rates of antidepressants are shown in Supplementary Figure 1. The elderly with MDD who did not take any antidepressants were included in the easy to treat group 1, and those who stayed on treatment with a single antidepressant were included in the easy to treat group 2. The definition of TRD varies; the most common definitions of TRD for MDD are (1) 1 or more treatment failures, (2) ≥ 2 treatment failures, and (3) ≥ 3 treatment failures.[22] Therefore, patients who poorly responded to the first adequate trial of antidepressant and then changed their antidepressant only once were included in the IDTT group. Patients whose antidepressant treatment regimens were altered 2 or more times were included in the DTT group. The DTT group was defined as TRD.[23] The combination of IDTT and DTT groups was defined as the TRT, which indicated a group whose response to the initial antidepressant treatment was poor. The examined psychiatric comorbidities were anxiety disorders, substance use disorders, and alcohol use disorders. The physical comorbidities were defined by calculating the score using the Charlson Comorbidity Index (CCI). The CCI is composed of 22 physical conditions (such as myocardial infarct, congestive heart failure, dementia, peripheral vascular disease, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, diabetes, leukemia, lymphoma, and malignant tumors) and indicated the physical condition of enrolled subjects.[24] Higher CCI scores indicated more severe physical conditions. We also assessed the level of urbanization (level 1 [most urbanized] to level 5 [least urbanized]) as a variable in this study.

Statistical Analysis

Logistic regression models with the adjustment of demographic data (age, sex, level of urbanization, and income), psychiatric comorbidities (anxiety disorders, substance use disorders, and alcohol use disorders), and the CCI score were performed to calculate the odds ratio (OR) and 95% confidence interval (CI) of TRD and TRT among the elderly with MDD. We also examined the individual OR

of TRD and TRT by stratifying by sex. Then, we examined the likelihood of TRD and TRT based on levels of physical condition (CCI score: 0, 1–4, ≥5) and income. A 2-tailed *P* value of less than .05 was considered statistically significant. All data processing and statistical analysis was performed using Statistical Package for Social Science (SPSS) Version 17 (SPSS Inc; Chicago, Illinois; 2008) and Statistical Analysis Software (SAS) Version 9.1 (SAS Institute; Cary, North Carolina; 2002).

Data Availability

As participants did not provide consent for their data to be publicly shared, even anonymized, data will be made available only to potential collaborators with ethical approval after they submit a research proposal to the Bureau of the National Health Insurance (NHI; https://nhird.nhri.org.tw/).

RESULTS

A total of 27,189 elderly patients with MDD were included in our study, and they had an average age of 72.12 ± 5.28 years; the majority were females (58.5%) (Table 1). During the first year of antidepressant treatment, 6,022 (22.1%) elderly patients failed to respond to the first antidepressant treatment and were classified as TRT, and 448 (1.6%) elderly patients developed TRD. Among the elderly patients with late-onset MDD, 16.6% had a diagnosis of anxiety disorders, 1.5% had alcohol use disorders, and 1.6% had substance use disorder. Only 4,513 (16.6%) patients had a CCI score of 0. There were 18,917 (69.5%) elderly patients with a CCI score of 1–4, and 3,933 (14.5%) with a CCI score ≥5. In addition, we found that the elderly with MDD who did not receive antidepressant treatment (easy to treat group 1) had lower total CCI scores than other 3 groups (1.99 ± 1.91 vs 2.47 ± 2.02 [easy to treat group 2] vs 2.62 ± 2.50 [IDTT] vs 2.64 ± 2.08 [DTT], *P* < .001).

Logistic regression models showed that TRD was associated with comorbidities of anxiety disorders (OR = 2.06; 95% CI, 1.67–2.53), substance use disorders (OR = 2.11; 95% CI, 1.26–3.53), and higher CCI scores (OR = 1.06; 95% CI, 1.01–1.10) (Table 2). Stratified by sex, in female patients TRD was associated with comorbid anxiety disorders (OR = 2.16; 95% CI, 1.67–2.80) and substance use disorders (OR = 3.76; 95% CI, 1.94–7.26), while in male patients TRD was associated only with comorbid anxiety disorders (OR = 1.89; 95% CI, 1.34–2.66). For TRT, logistic regression models showed that comorbid anxiety disorders (OR = 1.44; 95% CI, 1.34–1.55) and higher CCI scores (OR = 1.06; 95% CI, 1.05–1.08) were associated with a higher risk of TRT, and these associations were still observed when stratified by sex (Table 3). However, comorbid alcohol use disorders were not associated with TRD or TRT.

We then examined the severity of physical illness in association with TRD and TRT. Elderly patients with CCI scores ≥5 (OR = 1.68; 95%

Table 1. Demographic Data and Treatment-Resistant Depression Among the Elderly With Major Depressive Disorder

	Elderly With Major Depressive Disorder (n = 27,189)
Age at diagnosis, mean (SD), y	72.12 (5.28)
Sex, n (%)	
Female	15,895 (58.5)
Male	11,294 (41.5)
Level of antidepressant resistance, n (%)	
ETT-1	3,900 (14.3)
ETT-2	17,267 (63.5)
IDTT	5,574 (20.5)
DTT	448 (1.6)
Antidepressant-resistant depression (DTT), n (%)	448 (1.6)
Antidepressant-resistant tendency (IDTT+DTT), n (%)	6,022 (22.1)
Psychiatric comorbidities, n (%)	
Anxiety disorders	4,513 (16.6)
Alcohol use disorders	412 (1.5)
Substance use disorders	445 (1.6)
CCI score, mean (SD)	2.43 (2.02)
0, n (%)	4,337 (16.0)
1–4, n (%)	18,917 (69.5)
≥5, n (%)	3,935 (14.5)
Level of urbanization, n (%)	
1 (most urbanized)	4,700 (17.3)
2	7,709 (28.4)
3	2,464 (9.1)
4	3,432 (12.6)
5 (most rural)	8,884 (32.7)
Family income–related insured amount, n (%)	
< 19,100 NTD/mo	10,303 (37.9)
19,100–42,000 NTD/mo	11,269 (41.4)
> 42,000 NTD/mo	5,617 (20.7)

Abbreviations: CCI = Charlson Comorbidity Index, DTT = difficult to treat, ETT = easy to treat, IDTT = intermediate difficult to treat, NTD = new Taiwan dollar, SD = standard deviation.

Table 2. Logistic Regression of Antidepressant-Resistant Depression Among the Elderly With Major Depressive Disorder[a]

	Men OR (95% CI)	Women OR (95% CI)	Total OR (95% CI)
Psychiatric comorbidities			
Anxiety disorders	**1.89 (1.34–2.66)**	**2.16 (1.67–2.80)**	**2.06 (1.67–2.53)**
Substance use disorders	1.19 (0.52–2.73)	**3.76 (1.94–7.26)**	**2.11 (1.26–3.53)**
Alcohol use disorders	0.81 (0.30–2.20)	0.37 (0.05–2.69)	0.64 (0.26–1.57)
CCI score	1.06 (0.99–1.14)	1.05 (0.99–1.12)	**1.06 (1.01–1.10)**

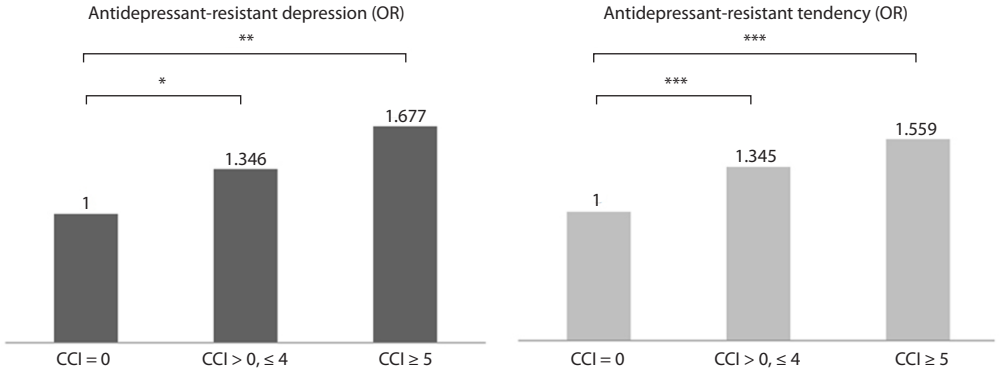
[a]Boldface type indicates statistical significance.
Abbreviations: CCI = Charlson Comorbidity Index, CI = confidence interval, OR = odds ratio.

Table 3. Logistic Regression of Antidepressant-Resistant Tendency Among the Elderly With Major Depressive Disorder[a]

	Men OR (95% CI)	Women OR (95% CI)	Total OR (95% CI)
Psychiatric comorbidities			
Anxiety disorders	**1.34 (1.19–1.50)**	**1.51 (1.38–1.66)**	**1.44 (1.34–1.55)**
Substance use disorders	1.17 (0.90–1.53)	1.32 (0.93–1.88)	1.23 (1.00–1.52)
Alcohol use disorders	1.01 (0.76–1.33)	0.77 (0.50–1.19)	0.92 (0.73–1.17)
CCI score	**1.07 (1.04–1.09)**	**1.06 (1.04–1.08)**	**1.06 (1.05–1.08)**

[a]Bold type indicates statistical significance.
Abbreviations: CCI = Charlson Comorbidity Index, CI = confidence interval, OR = odds ratio.

Figure 1. Likelihood of Antidepressant-Resistant Depression and Antidepressant-Resistant Depression Among Adults With Major Depressive Disorder, Stratified by CCI Score



*P < .05. **P < .01. ***P < .001.
Abbreviations: CCI = Charlson Comorbidity Index, OR = odds ratio.

CI, 1.18–2.39) and CCI scores of 1–4 (OR = 1.35; 95% CI, 1.00–1.81) were more likely to develop TRD than those with a CCI score of 0. Patients with CCI scores ≥ 5 (OR = 1.56; 95% CI, 1.40–1.74) and CCI scores of 1–4 (OR = 1.35; 95% CI, 1.24–1.47) were also more likely to develop TRT than those with a CCI score of 0 (Figure 1).

DISCUSSION

To our knowledge, this is the first nationwide population-based cohort study to investigate the association between early TRT and late-onset MDD. We found that during the first year of treatment, 22% of elderly patients with late-onset MDD failed to respond to the first adequate trial of antidepressant treatment, and approximately 1.6% met the criteria of TRD. Comorbid anxiety disorders and substance use disorders were associated with 106% and 111% of increased risks of TRD, respectively, and an increase in CCI score of 1 was associated with 6% of increased risk of TRD. For TRT, comorbid anxiety disorders were associated with 44% of increased risk of TRT, and an increase in CCI score of 1 was associated with 6% of increased risk of TRT. Taken together, although both physical and psychiatric comorbidities were associated with early TRT in patients with late-onset MDD, comorbid anxiety disorders and substance use disorders were more associated with TRT and TRD than comorbid physical illnesses.

Few studies have examined the incidence of TRT and TRD during the first year of late-onset MDD. TRD is not an uncommon condition in clinical practice, with 50%–60% of patients not achieving adequate response following antidepressant treatment.[23] For late-onset MDD, previous studies suggest that TRD develops in one-third of elderly patients during their lifelong course of MDD.[8,9] Our study focused on early TRT in patients with late-onset MDD. We found that 22% of elderly patients could not respond to an adequate trial of antidepressant treatment, and 1.6% of elderly patients developed TRD during the first year of late-onset MDD. Some patients with TRT or TRD might be excluded if they did not receive adequate dose of antidepressants > 60 days during the first year of treatment.

We found that early TRT in late-onset MDD was associated with comorbid anxiety disorders. Comorbid anxiety disorders have been reported to lower the effect of treatment in MDD.[25] Among elderly patients with MDD, anxiety disorders are the most common type of comorbid mental health disorders.[26] Importantly, rates of somatic symptoms, disability, and suicide are higher in elderly patients with MDD and anxiety disorders than in those without comorbid anxiety disorders.[27,28] Moreover, the risk of cognitive decline was higher in elderly patients with both MDD and anxiety disorders than those with MDD alone.[29] Cognitive decline may limit the effectiveness of treatment for depression and further leads to the occurrence of TRT or TRD.[30]

We also found that comorbid substance use disorders were associated with an increased risk of early TRT in elderly patients with late-onset MDD. Previous studies have suggested that substance use disorders are associated with a higher risk for subsequent TRD, while TRD is also associated with an elevated risk for subsequent substance use disorders.[31,32] Few studies have addressed the association between late-onset TRD and comorbidity with substance use disorders in older adults, although evidence suggests a high correlation between MDD and substance use disorders in the population.[33] The co-occurrence of MDD and substance use disorder may complicate the diagnosis and treatment of both. For example, a recent study reported that substance use–related impairment was strongly associated with treatment response among the elderly with MDD.[34] However, the lack of association of TRT and TRD with alcohol use disorder may be attributed to a greater likelihood of dropout or adherence failure among these patients.

Chronic physical illness is consistently associated with an increased prevalence of depressive symptoms and disorders.[35,36] In contrast, late-onset MDD frequently develops in the context of medical morbidities, such as heart disease/stroke (vascular etiology), dementia

(neurodegenerative illness), or multimorbidity, and chronic inflammation.[37] Our study found that patients with late-onset MDD and CCI scores of 1–4 and ≥ 5 were more likely to develop TRD and TRT compared to those with a CCI score of 0. This finding suggests that although comorbid physical illnesses are common in late-onset MDD, there is still an association with early TRT. Indeed, the global burden of physical illness is a strong predictor of poor depressive outcome.[38] Recognizing and treating comorbid physical illnesses is important for patients with late-life MDD. Comorbid physical illnesses may negatively affect tolerance and treatment response; therefore, the management of physical illnesses needs to be considered an integral part of treatment strategies for patients with late-onset MDD who develop TRD. However, among patients with late-onset MDD, the associations of early TRD with psychiatric comorbidities (eg, anxiety disorders and substance use disorders) were more obvious than those with physical comorbidities, and these associations were also observed in early TRT.

This study had several limitations that should be addressed. First, some information, such as the severity of depression, family history, environmental factors, and the reasons that patients did not receive antidepressant treatment (ie, easy to treat group 1), were unavailable in the Taiwan NHIRD. Without this information, we could not evaluate the effects of these factors on TRT among the elderly with MDD. We addressed this issue by adjustment of demographic data in our statistical models. Second, clinical rating scales for depression were not available in the database. Following the definition of previous studies based on NHIRD,[21,39,40] we defined the treatment response based on the use and prescription pattern of antidepressants. Failure to respond to the first trial of antidepressant treatment with optimal dosage (ie, fluoxetine ≥ 20 mg/d) and treatment duration of > 60 consecutive days and switching to a second trial of antidepressant treatment was defined as non-responsiveness in the current study. The diagnostic validity of TRD in our study has been considered acceptable in previous studies.[21,39,40] Third, TRD has been associated with an increased risk of dementia in patients, and the risk was highest in elderly patients with MDD.[40] Therefore, the early TRT in patients with late-onset MDD might be associated with underlying dementia. However, this confounding factor was addressed by adjusting for CCI score, which included the condition of dementia. Fourth, the low incidence of TRD during the first year of late-onset MDD might be related to differences in study populations, and data for augmentation treatment for partial responders were not included. Fifth, we combined all anxiety disorders as a single category of anxiety disorder in the regression models. Whether different anxiety disorders, such as panic disorder, specific phobia, and generalized anxiety disorder, may differentially affect treatment response in geriatric depression would need further investigation. Finally, the NHI was implemented in 1995, and we could obtain only approximately 25 years of data for the participants.

In conclusion, this is the first national study to examine the association of physical and psychiatric comorbidities with early antidepressant resistance in elderly patients with late-onset MDD. We conclude that although both physical and psychiatric comorbidities were associated with early TRT among patients with late-onset MDD, psychiatric comorbidities are more associated with an increased risk of TRD or TRT. Our findings may serve as a reminder to clinicians to be aware of possible psychiatric comorbidities, particularly anxiety and substance use disorders, when reporting poor treatment response to antidepressants in elderly patients with late-onset MDD during the first year of treatment.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Early Antidepressant Resistance in Late-Onset Major Depressive Disorder: A Nationwide Population-Based Cohort Study

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List of Supplementary Material for the article

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Supplementary Table 1. Usual daily dosage of antidepressant medications

Drug Class	Recommended Dose Range (mg)
Citalopram	20-40
Escitalopram	10-20
Fluoxetine	20-60
Fluvoxamine	100-300
Paroxetine	20-60
Sertraline	50-200
Venlafaxine	75-375
Duloxetine	30-120
Milnacipran	100-200
Bupropion	150-450
Mirtazapine	15-60

Reference: Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Synopsis of Psychiatry 11th, North American Edition.

Supplementary figure 1. Prescription rate of antidepressants