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Risk of Suicide in Patients With Major Depressive Disorder and Comorbid Chronic Pain Disorder: An Insight From National Inpatient Sample Data

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Background: Approximately 17.3 million adults in the United States have had a minimum of one major depressive episode. Comorbidity of depression and pain can affect individuals of any age, but is more prevalent in the elderly affecting up to 13% of people in the elderly population. Given that depression and suicidal ideation (SI) pose a considerable burden resulting in enormous suffering, there is a need to understand the factors of the relationship between chronic pain (CP), depression, and SI.

Objectives: Our primary objective in this study was to compare suicidality (SI/attempt [SA]) between patients with major depressive disorder (MDD) and CP and a matched control group. The secondary objective was to compare length of stay, total hospital costs, and discharge disposition in these populations.

Study Design: The National Inpatient Sample (NIS) dataset developed by the Healthcare Cost and Utilization Project was used for this study. The NIS is a database of hospital inpatient stays derived from billing data submitted by hospitals to statewide data organizations across the United States. We obtained patient records from the NIS dataset for the years 2006 to 2017. All data were de-identified so Institutional Review Board approval was waived.

Methods: We used mean and standard error to describe continuous data and counts (percentage) to describe categorical data. Categorical data were compared using Rao-Scott adjusted chi-square tests and continuous data were compared using Student's t tests. Matching was performed using propensity scores in random order with a caliper size of 0.001. To assess predictors associated with suicidality, logistic regression analysis was performed.

Results: A total of 393,481 patients having MDD with CP (MDD+CP) were included in the analysis. The mean age was 49.4 years, and 54.9% of patients were women. Overall, rate of composite outcome of SI/SA was more prevalent in MDD+CP group (51% vs 41%, $P < 0.001$). Rate of SI was 48% vs 39% ($P < 0.001$) in the MDD+CP and MDD without CP (MDD-CP) groups, respectively. MDD+CP was one of the strongest predictors of suicidality, responsible for 48% more risk of SI/SA compared to MDD-CP group. In comparison to non-Whites, the rate of suicidality was 7.5% less in White population. Alcohol abuse and substance abuse were associated with 16% and 7% greater risk of SI/SA, respectively. For women, the odds of having SI/SA was 1.20 greater compared to men.

Limitations: No information was available on the causal relationship between MDD+CP disorder and SI/SA. Retrospective studies are susceptible to recognition, reporting, and coding bias. There is no information available on medications use or the duration and severity of CP and bipolar disorder, which can all be confounding factors.

Conclusions: Psychiatrists and other physicians must be cognizant of the presence of CP and the risk of suicide, especially when patients present with depressive symptoms. The treatment plan for this patient population should include routine screening for pain symptoms and risk assessment for SI.

Key words: Chronic pain, suicidality, suicide, major depressive disorder, opioid use disorder, self

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harm, anxiety, inpatient

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Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition categorizes depressive disorders according to duration, timing, and presumed etiology. The symptoms of depressive disorders consist of low mood, diminished interest, anhedonia, weight change, sleep disruption, psychomotor agitation, fatigue, feelings of worthlessness or guilt, low concentration, and suicidal ideation (SI), which should last for at minimum of 2 weeks. Such symptoms cause significant distress and impairment in social and occupational functioning (1). Approximately 17.3 million adults in the United States have had a minimum of one major depressive episode. The prevalence of major depressive episodes is higher among women (10.5%) compared to men (6.2%) (2). Depression is a well-known risk factor for chronic pain (CP) (3).

Comorbidity of depression and pain can affect individuals of any age, but is more prevalent in the elderly affecting up to 13% of people in the elderly population (3). High rates of depression among patients with CP and co-occurring other psychopathology have important treatment implications (4-5). According to a study in a Canadian population, the prevalence of depression is 3 times greater in those with chronic back pain than without CP (6). Overall, patients with CP have a 30% to 40% prevalence of major depression (7).

Suicide and self-harm are also common symptoms that present with major depressive disorder (MDD). Data from 2020 suggested more than 45,900 Americans died by suicide, indicating a rise in suicide attempts (SAs) and overall deaths (8,9). In one study (10) performed in outpatient hospitals in China, the prevalence of MDD and one-month prevalence of suicidality were 3.7% and 2.3%, respectively.

Pain tolerance is decreased in major depression, and somatic preoccupation can be a prominent symptom, especially in older people. Of note, more than half of the patients presenting with major depression in primary care report some pain (11). In many cases, diagnosis is delayed, especially when the diagnosis of depression is imprecise. Another proposed mechanism for the relationship is that CP represents a subtype of depression (12). This is supported by studies (13-15) showing that serotonergic and noradrenergic neurotransmitters are involved in both conditions, and treatments effective for depression are often effective for pain (e.g., opioids, ketamine, antidepressants, electroconvulsive therapy). However, there is little clinical evidence to support this notion. Based on the above-mentioned risk factors, it is not surprising that MDD is associated with a significantly elevated risk of early death (13). This is not solely because people with MDD have an elevated suicide risk (14-15), but because depression is associated with an elevated risk of onset, persistence, and severity of a wide range of physical and mental disorders. Despite advances in the treatment among patients with depression, suicide risk is still high. Hence, it is important to target other factors, such as pain condition, which are not routinely addressed during the assessment (29).

Given that depression and CP disorders (CPDs) are interrelated, there is a need to understand the factors the of the relationship between CP, depression, and SI. Our primary objective was to compare suicidality (SI/SA) between patients with MDD and CP and a matched control group. The secondary objective was to compare length of stay, total hospital costs, and discharge disposition in these populations.

Methods

The National Inpatient Sample (NIS) dataset (16) developed by the Healthcare Cost and Utilization Project was used for this study. The NIS is a database of hospital inpatient stays derived from billing data submitted by hospitals to statewide data organizations across the United States. These inpatient data include clinical and resource use information typically available from discharge summaries. The NIS dataset contains more than 7 million hospital stays each year. There is a discharge-level weight applied to each record to create national estimates of inpatient hospitalization. Each record contains information on age, gender, race, comorbidities, hospital diagnosis, hospitalization charges, length of stay, hospital location, primary insurance, admission month, admission day of the week, and discharge disposition. In the dataset, all diagnoses are stored in the dataset based on International Classification of Diseases, Ninth Revision, Clinical Modification/

Procedure Coding System (ICD-9-CM), and International Classification of Diseases, Clinical Modification, Procedure Coding System (ICD-10-CM/PCS).

We obtained patient records from the NIS dataset for the years 2006 to 2017. All data were de-identified so Institutional Review Board approval was waived.

For data collection, we obtained our study cohort by performing a query for all the adult patients (age ≥ 18), with MDD as a primary indication of admission and comorbid CPDs (MDD+CP group). We selected MDD patients by using ICD-9 codes "29620-29626, 29630-29636" and ICD-10 codes "F320-F325, F329-F333, F3340-F3342, F339" (Supplemental Table 1). For CPDs, we used ICD-9 codes "33821, 33822, 33828, 33829, 3384" and ICD-10 codes "G8921, G8922, G8928, G8929, G894" (Supplemental Table 1). For the comparison control group, we selected patients with primary diagnosis of MDD without comorbid CPDs (MDD-CP group). To reduce the imbalance between the groups, we matched the control group based on age, gender, and primary diagnosis. In addition, we collected data on race, SI/SA, substance and alcohol abuse, opioid use disorders, and hypothyroidism (Table 1).

Statistical Analysis

We used mean and standard error (SE) to describe continuous data and counts (percentage) to describe categorical data. Categorical data were compared using Rao-Scott adjusted chi-square tests and continuous data were compared using Student's t tests. To control for potential imbalance between groups, we performed 1:1 matching by age, gender, and primary diagnosis code. Matching was performed using propensity scores in random order with a caliper size of 0.001. To assess predictors associated with suicidality, logistic regression analysis was performed. In the multivariate analysis age, gender, race, drug abuse, alcohol abuse, and MDD+CP were included (Table 2). Variance inflation factors were used to detect collinearity. Since 15% of race data were missing, we analyzed it as a separate category. Odds ratios (OR) and 95% confidence intervals (CI) were used to present the results of logistic regression analysis. All calculations were performed by complex survey data analysis techniques using appropriate strata, cluster, and weight variables provided in the NIS dataset. The statistical analysis was performed using SAS software version 9.2 (SAS Institute Inc., Cary, NC) and SPSS version 26.0 software for Windows (IBM Corporation, Armonk, NY). All tests were 2-sided, with a P value < 0.05 considered statistically significant.

Table 1. *Baseline patient and hospital characteristics of study population.*

	MDD without CPD (n = 390,967)	MDD with CPD (n = 393,481)	*P* value
Patient Level Characteristics			
Age			
Mean, SE	49.2 (0.10%)	49.4 (0.10%)	0.06
Gender			
Men	177,866 (45.5%)	177,269 (45.1%)	0.13
Women	213,101 (54.5%)	216,212 (54.9%)	
Race			< 0.001
White	254,524 (74.9%)	285,252 (82%)	
Black	43,699 (12.9%)	32,093 (9.2%)	
Hispanic	26,561 (7.8%)	20,401 (5.9%)	
Asian or Pacific Islander	3,308 (1%)	2,133 (0.6%)	
Native American	2,111 (0.6%)	2,342 (0.7%)	
Other/ Unknown	9,430 (2.8%)	5,804 (1.7%)	
Comorbidities			
Psychotic Disorders	13,482 (3.4%)	12,715 (3.2%)	0.03
Anxiety Disorders	143,972 (36.8%)	184,010 (46.8%)	< 0.001
Opioid Use Disorders	32,693 (8.4%)	79,441 (20.2%)	< 0.001
Alcohol Abuse	107,785 (27.6%)	89,338 (22.7%)	< 0.001
Substance Abuse	128,989 (33.0%)	180,141 (45.8%)	< 0.001
Hypothyroidism	38,868 (9.9%)	44,266 (11.2%)	< 0.001
Primary Payer			< 0.001
Medicare/ Medicaid	202,313 (51.7%)	244,028 (62%)	
Self-pay/Other	59,233 (15.2%)	51,157 (13%)	
Private Insurance	129,421 (33.1%)	98,297 (25%)	
Hospital Region			< 0.001
Northeast	85,298 (21.8%)	58,612 (14.9%)	
Midwest	113,426 (29%)	108,316 (27.5%)	
South	146,462 (37.5%)	170,024 (43.2%)	
West	45,781 (11.7%)	56,529 (14.4%)	
Disposition			0.25
Routine	343,155 (87.8%)	345,073 (87.7%)	
Other Health Care Facility	42,553 (10.9%)	42,758 (10.9%)	

Table 1 (cont.). *Baseline patient and hospital characteristics of study population.*-

	MDD without CPD (n = 390,967)	MDD with CPD (n = 393,481)	*P* value
Against Medical Advice	5,107 (1.3%)	5,547 (1.4%)	
Died	152 (0%)	103 (0%)	
Length of Hospital Stay, Days	6.67 (0.05%)	6.70 (0.05%)	0.49
Total Cost, $	17,778 (206)	18,852 (216)	< 0.001

*15% of the race data were missing.
Abbreviations: MDD, major depressive disorder; CPD, chronic pain disorder; SE, standard error.

Results

Baseline Characteristics

A total of 393,481 patients having MDD+CP were included in the analysis. The mean age was 49.4 years, and 54.9% of patients were women. In the MDD-CP control group (n = 390,067), the mean age was 49.2, and 54.5% patients were women (Table 1). To avoid the imbalance between the groups, we matched 2 groups for age, gender, and primary diagnosis category. In the matched cohort 393,481 patients were included in MDD+CP group and 390,967 patients were included in MDD-CP group.

Baseline characteristics are shown in Table 1. Eighty-two percent of patients were White in the MDD+CP group and 74.9% of patients were White in the MDD-CP group. There were higher proportions of Hispanics and Blacks in the MDD-CP group. Opioid use disorders were more common in the MDD+CP group (20.2% vs 8.4%, $P < 0.001$) as were anxiety disorders were more common in the MDD+CP group (46.8% vs 36.8%, $P < 0.001$). In the MDD-CP group, alcohol abuse was more prevalent (27.6% vs 22.7%, $P < 0.001$). Hypothyroidism and d substance abuse were more prevalent in the MDD+CP group.

Among hospital characteristics, the majority of the MDD+CP patients had Medicare/Medicaid as their primary payer, when compared to MDD+CP more patients in the MDD-CP group carried private insurance. Regionally, MDD+CP was more common in Southern and Midwestern parts of the United States. There were no significant differences in discharge disposition or length of stay between groups. However, the total cost of hospitalization was higher in MDD+CP group ($18,852 vs $17,778, $P < 0.001$).

Table 2. *Multivariate logistic regression analysis for factors associated with suicidality.*

Variables	Multivariate Analysis	
	OR (95% CI)	*P* value
Age, per 5 years increase	0.93 (0.92-0.93)	< 0.001
Women	1.20 (1.18-1.23)	< 0.001
White Race	0.92 (0.88-0.97)	< 0.001
Alcohol Abuse	1.16 (1.13-1.19)	0.003
Drug Abuse	1.07 (1.04-1.10)	< 0.001
MDD+CPD	1.475 (1.424-1.528)	< 0.001

Abbreviations: OR, odds ratio; CI, 95% confidence interval; MDD, major depressive disorder; CPD, chronic pain disorder.

Predictor of Suicide and Rate of Suicidality

Overall, rate of composite outcome of SI/SA was more prevalent in the MDD+CP group (51% vs 41%, $P < 0.001$) (Fig. 1). Rate of SI was 48% vs 39% ($P < 0.001$) in the MDD+CP and MDD-CP groups, respectively. There was no difference in the SA rate between the groups (3.8% vs 3.7 %, $P = 0.86$). In the logistic regression analysis, age, women, White race, alcohol abuse, drug abuse, and MDD+CP were included as predictors and SI/SA as an outcome (Table 2). MDD+CP was one of the strongest predictors of suicidality, responsible for 48% more risk of SI/SA compared to the MDD-CP group. Each 5-year increase in age was associated with 7% less risk of SI/SA. In comparison to non-Whites, the rate of suicidality was 7.5% less in White people. Alcohol abuse and substance abuse were associated with 16% and 7% greater risk of SI/SA, respectively. For women, the odds of having SI/SA was 1.20 greater compared to men.

Discussion

MDD and CP are frequently co-prevalent, and the 2 disorders share demographic, clinical, and neurobiological similarities (17). Understanding the relationship between these factors and their shared pathophysiology can aid health care providers in identifying people who are suffering from CP and are at risk of suicide, as well as implementing individualized, integrated programs to treat them (18). To our knowledge, this study is first to investigate the risk of suicidality in patients with MDD having comorbid CPD using a large NIS dataset. We compared the MDD+CP and MDD-CP groups. In baseline characteristics, the majority of patients were White race in both groups, with Hispanics and Blacks being more prevalent in the MDD-CP group. The MDD+CP group had higher rates of opioid use and anxiety disorders, while the MDD-CP group had higher rates of alcohol misuse. Medical comorbidities, such as hypothyroidism and substance

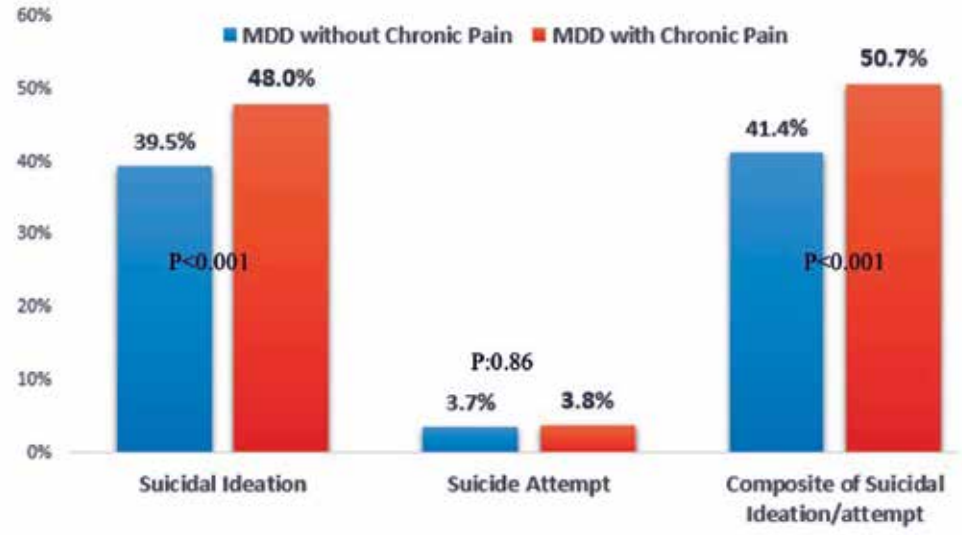

Fig. 1. *Rate of SI/SA between the groups.*
SI/SA, suicidal ideation/attempt.

abuse, were also more prevalent in the MDD+CP group. Although there were no significant differences between the groups in terms of discharge disposition or length of stay, the MDD+CP group had higher hospitalization costs (Table 1).

SI was more common in the MDD+CP group than in the MDD-CP group. There was no difference between groups when it came to SAs. MDD+CP was one of the strongest predictors of suicidality in our study. Alcohol and substance abuse, women, non-White racial background, and younger age were also linked to a higher incidence of SI/SA.

Nicholl et al (19) in their cross-sectional study, investigated the prevalence of CP and depression by ethnic groups and found comorbid CP and depression were more common in Whites (11.1%) compared to Asians (7.5%) and Blacks (8.5%). They concluded that this could be due to cultural differences and language obstacles, which might make it difficult for minority ethnic groups to receive quality care. Equally, in our study population, majority of patients were of the White race in both groups.

Arnow et al (20) found that patients with comorbid depression and debilitating CP had considerably lower health-related quality of life, more severe somatic symptoms, and a higher prevalence of panic disorder than those without comorbid depression or CP. CP has been shown in studies (17,36) to cause (and be exacerbated by) depression, engender hopelessness, facilitate a desire for death as an escape, and erode the natural fear of death.

According to research (21) into the possible factors responsible for the deterioration of treatment gains in patients with CP after completion of treatment, depression was more common among individuals who had a poorer treatment response. Proctor et al (22) found that the patients' self-medication attempts to achieve greater pain relief accounted for most reported reasons for taking more than the prescribed dosage of the medications. Also, CP patients have high rates of SI and SA, and access to prescription opioids increases the risk of suicide death in this patient population (23).

On average, 65% of patients with depression have one or more pain complaints, while depression is prevalent in 5% to 85% of patients with CP conditions (depending on the study environment) (24). According to current evidence, those who suffer from CP are more likely to suffer from a variety of negative health outcomes, including suicide. Several predictive factors, such as pain severity, pain interference, duration of pain, and specific pain diagnoses (cancer pain vs non-cancer pain), were identified, which may increase the risk of suicidal behavior (25-29). Roughan et al (30) observed that SI was more common in depressed patients with concurrent CP (OR = 1.49 [CI, 1.38-1.61]) than those without CP, and a recent attempt at suicide was linked to persistent pain (OR = 1.88 [CI, 1.14-3.09]). Recent suicidal thoughts and SA were similarly positively

linked with CP severity (30). In our study, although we did not evaluate the magnitude of pain, CP by itself was the strongest predictor of suicidality.

Studies (31-32) have found that taking analgesic and anxiety medications (such as benzodiazepines) at the same time, as well as having an alcohol use disorder or mood illness while on prescription pain medications, can all enhance the risk of suicide among CP patients. In our study, we found that abuse of alcohol and illicit drugs was associated with a 16% and 7% increased risk of SI/SA, respectively, in the MDD+CP group. As noted above, psychotropic medications, such as antidepressants and ketamine, as well as nonpharmacological interventions, such as repetitive transcranial magnetic stimulation and electroconvulsive therapy, can be beneficial for CP, as well as underlying mood or anxiety disorders (33-37).

Several limitations should be considered when interpreting these findings. Since this is a cross-sectional retrospective study, no information was available on the causal relationship between MDD+CPD and SI/SA. Retrospective studies, whether they are chart reviews at academic institutions or hospital claims data (as in our case), are susceptible to recognition, reporting, and coding bias. Because our study makes use of a de-identified administrative database, it is susceptible to coding errors that cannot be individually verified. Due to the fact that the records in the dataset are discharge summaries rather than individual patients, it is possible that some patients with multiple admissions were counted more than once. Last, there is no information available on medications used or the duration and severity of CP and MDD, which can all be confounding factors.

Conclusions

Psychiatrists and other physicians must be cognizant of the presence of CP and the risk of suicide, especially when treating patients present with depressive symptoms. The treatment plan for this patient population should include routine screening for pain symptoms and risk assessment for SI. If a patient is ascertained to be at a high risk of self-injury, an individualized plan of action should be established to mitigate this risk. Contact information for local psychiatric emergency services should be included in this plan.

Supplemental table available at www.painphysicianjournal.com

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Supplemental Table 1. ICD-9 and ICD-10 used to obtain the study population.

ICD-9 and ICD-10 Codes	MDD
29620	Major depressive affective disorder, single episode, unspecified
29621	Major depressive affective disorder, single episode, mild
29622	Major depressive affective disorder, single episode, moderate
29623	Major depressive affective disorder, single episode, severe, without mention of psychotic behavior
29624	Major depressive affective disorder, single episode, severe, specified as with psychotic behavior
29625	Major depressive affective disorder, single episode, in partial or unspecified remission
29626	Major depressive affective disorder, single episode, in full remission
29630	Major depressive affective disorder, recurrent episode, unspecified
29631	Major depressive affective disorder, recurrent episode, mild
29632	Major depressive affective disorder, recurrent episode, moderate
29633	Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior
29634	Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior
29635	Major depressive affective disorder, recurrent episode, in partial or unspecified remission
29636	Major depressive affective disorder, recurrent episode, in full remission
F320	Major depressive disorder, single episode, mild
F321	Major depressive disorder, single episode, moderate
F322	Major depressive disorder, single episode, severe without psychotic features
F323	Major depressive disorder, single episode, severe with psychotic features
F324	Major depressive disorder, single episode, in partial remission
F325	Major depressive disorder, single episode, in full remission
F329	Major depressive disorder, single episode, unspecified
F330	Major depressive disorder, recurrent, mild
F331	Major depressive disorder, recurrent, moderate
F332	Major depressive disorder, recurrent, severe without psychotic features
F333	Major depressive disorder, recurrent, severe with psychotic symptoms
F3340	…… unspecified
F3341	Major depressive disorder, recurrent, in partial remission
F3342	Major depressive disorder, recurrent, in full remission
F339 {AU: Move?/ Insert after "F333" above?}	Major depressive disorder, recurrent, unspecified
ICD-9 and ICD-10 Codes	CP
33821	CP due to trauma
33822	Chronic post-thoracotomy pain
33828	Other chronic postoperative pain
33829	Other CP
3384 {AU: "3384?"/Missing digit?}	CP syndrome
G8921	CP due to trauma
G8922	Chronic post-thoracotomy pain
G8928	Other chronic post-procedural pain
G8929	Other CP
G894 {AU: "G894?"/Missing digit?}	CP syndrome

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; MDD, major depressive disorder; CP, chronic pain.