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The Mediating Effect of Sleep Disturbance on the Relationship Between Nonmalignant Chronic Pain and Suicide Death

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Abstract

Importance: Few studies have examined the relationship between nonmalignant chronic pain (NMCP) and suicide death, and even fewer have specifically explored what role sleep disturbance might play in the association between NMCP and suicide death.

Objective: To assess whether sleep disturbance mediates the relationship between NMCP and suicide death.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

Design: This case-control study included 2,674 individuals who died by suicide between 2000 and 2013 (cases) and 267,400 matched individuals (controls).

Setting: Eight Mental Health Research Network (MHRN)-affiliated healthcare systems.

Participants: All cases and matched controls were health plan members for at least 10 months during the year prior to the index date.

Main Outcomes and Measures: Sociodemographic data and diagnosis codes for NMCP and sleep disorders were extracted from the MHRN's Virtual Data Warehouse. Suicide mortality was identified using International Statistical Classification of Diseases and Related Health Problems (ICD)-10 codes from official government mortality records matched to health system records.

Results: After accounting for covariates, there was a significant relationship between NMCP and sleep disturbance; those who were diagnosed with NMCP were more likely to develop subsequent sleep disturbance. Similarly, sleep disturbance was significantly associated with suicide death. Finally, a significant indirect effect of NMCP on suicide death, through sleep disturbance, and a nonsignificant direct effect of NMCP on suicide death provide support for a fully mediated model.

Conclusions and Relevance: There is a need for clinicians to screen for both sleep disturbance and suicidal ideation in NMCP patients and for health systems to implement more widespread behavioral treatments that address comorbid sleep problems and NMCP. ■

Keywords

sleep; suicide; chronic pain

INTRODUCTION

Suicide is the tenth leading cause of death among Americans, and more than 44,000 people died by suicide in 2015 the United States.¹ In addition to significant financial costs to society (over \$56.9 billion a year in combined medical and work-related costs),² suicide results in profound personal costs for surviving friends and family members. Evidence suggests that surviving the loss of a loved one to suicide is in and of itself a risk factor for suicide. Additional risk factors for suicide include a family history of suicide, a family history of maltreatment, and a history of mental health diagnoses, including depression and substance abuse.³

Prior research also suggests that chronic pain and sleep disturbance are risk factors for suicide. Recent studies have found that chronic pain patients have twice the risk for death by suicide, compared to those without chronic pain,⁴ and 50% of chronic pain patients reported that they had considered suicide at some point due to their pain.⁵ Similarly, one recent study reported persistent insomnia and poor sleep quality to be a strong predictor of suicidal ideation⁶; results from another study indicated that poor sleep quality increased the risk for suicide by approximately 34%.⁷ These findings are particularly concerning given the prevalence of chronic pain and sleep disturbance in the United States: the 2012 National Health Interview Survey found that nearly 25 million U.S. adults suffer from daily chronic pain,⁸ and the Centers for Disease Control and Prevention (CDC) estimates that 50 million to 70 million U.S. adults have chronic sleep and wakefulness disorders.⁹

Interestingly, there is increasing evidence that these risk factors for suicide may be interrelated. Smith et al.¹⁰ found that chronic pain patients with insomnia/sleep disturbance were more likely to report suicidal ideation compared to patients without sleep problems. Triñanes et al.¹¹ found that chronic pain patients with suicidal ideation reported more daytime dysfunction related to sleep compared to patients without suicidal ideation. Calandre et al.¹² found that suicide attempters with fibromyalgia reported poorer quality sleep compared to nonattempters. Two other studies similarly have reported that poor sleep quality among individuals with chronic pain was predictive of suicidal ideation.^{13,14} Evidence suggests that individuals with chronic pain may experience presleep arousal and pain-related intrusive thoughts leading to insomnia¹⁵⁻¹⁷; insomnia, in turn, can lead to hopeless/helpless attitudes¹⁸ and deficient problem-solving/coping,¹⁹⁻²¹ which may increase suicide risk. Though these studies provide initial evidence supporting the associations between chronic pain, insomnia/sleep disturbance, and suicide, they have been limited by several factors, including small sample sizes, lack of control of important confounders (eg, comorbid mental illness), cross-sectional designs, and a focus only on suicidal ideation and attempt rather than suicide death.⁶ Therefore, the purpose of the present study was to assess whether sleep disturbance mediates the relationship between nonmalignant chronic pain and suicide death, controlling for relevant confounders, in a large case-control study.

METHODS

Study Population and Setting

The sample included 2,622 individuals who died by suicide between 2000 and 2013 (cases) and 266,191 matched individuals (controls). The date of suicide for cases was considered the index date, and all matched controls were assigned the same corresponding index date (cases and controls matched by time period and site). All individuals had been health plan members for at least 10 months during the year prior to the index date. The process of matching cases and controls is described in more detail in an article by Ahmedani et al.²² The health plans were aligned with 8 large Mental Health Research Network (MHRN)-affiliated healthcare systems located across the United States. The combination of both health plan and health system membership data allowed comprehensive capture of both electronic health records and insurance claims data from within and outside of the healthcare system. Health plan membership included commercial, Medicaid, Medicare, and self-pay insurance plans, representing a diverse range of plans.

Data Sources and Measures

Suicide mortality was identified using International Statistical Classification of Diseases and Related Health Problems (ICD)-10 codes (X60-X84, Y87.0) from official government mortality records matched to health system records, using the definition and coding process developed by the CDC. ICD-9 diagnosis codes were extracted from the MHRN's Virtual Data Warehouse (VDW), which is a federated data model in each health system, including a combination of electronic health record and insurance claims organized in the same format using the same variables and data definitions across health system sites. Data on encounters, pharmacy fills, diagnoses, medical tests, demographics, and costs are organized using the same definitions across sites and are quality checked locally.²³ Sleep disturbance was

defined as having a sleep disorder diagnosis (ICD-9 codes 291.82, 307.4, 327, 780.5). Chronic, noncancer pain included any 2 pain diagnoses occurring between 3 and 12 months apart within the same diagnostic cluster (back pain [ICD-9 codes 720.0-724.9], fibromyalgia [ICD-9 code 729.1], migraine [ICD-9 code 346], psychogenic pain [ICD-9 codes 307.8, 307.89], neuropathy [ICD-9 code 350.0-350.9, 356.0-356.9], other headache [ICD-9 code 339.0-339.9], or arthritis [ICD-9 codes 714.0-716.9], without a cancer diagnosis). Diagnosis codes for noncancer chronic pain and sleep disturbance occurring within the 1-year period prior to the index date were consistent with standard definitions, as described in more detail in an article by Ahmedani et al.²² To account for temporal ordering and maximize confidence in our results, individuals who had a diagnosed sleep disorder before the occurrence of chronic pain ($n = 312$; 0.12% of the sample) were eliminated from the analyses. Mental health and substance use diagnoses (ICD-9 codes 290 to 319) were also captured. The reader is referred to the MHRN website (<https://github.com/MHResearchNetwork/MHRN-Central>) for additional details regarding the specific mental health diagnoses included.

Demographic information on age (<18, 18 to 64, or 65+ years) was available from the VDW. For each person, estimated neighborhood income was calculated using geocoded addresses and census block data. Race and ethnicity data were not available for several sites prior to 2008; thus, these variables were not included in the study.

Analyses

We conducted bivariate analyses using SAS version 9.4 (SAS Institute, Cary, NC, U.S.A.) and a path analysis with tests for mediation using MPlus version 7.4.²⁴ Path models were estimated using theta parameterization and a weighted least-squares estimator with robust standard errors per the MPlus model guidelines for testing binary mediators and outcomes.²⁵ This approach utilizes a probit model, which examines binary outcomes as continuous latent response variables and treats predictors as linear and representing an increase or decrease in the probability of the outcome.²⁵ As such, probit regression coefficients indicate the change in probit index for a 1-unit change in the predictor. Per the recommendations for path models with categorical variables,²⁵ we generated bootstrap standard errors and 95% confidence intervals using 1,000 estimates. Parameter estimates for indirect effects were calculated using the product of coefficients method via the model indirect statement in MPlus.²⁶ The model (Figure 1) included paths from chronic pain to both sleep disturbance and suicide death, as well as from sleep disturbance to suicide death. The model included measurement of the indirect path from chronic pain to suicide death (dashed line in figure). Analyses controlled for effects of income, age, and past year mental health disorder, as these were variables identified as possible confounders in prior studies.^{12,27-29}

RESULTS

A total of 268,813 individuals (2,622 cases, 266,191 controls) were included in the analyses. As described in Table 1, individuals who died by suicide were nearly twice as likely as controls to be diagnosed with chronic pain ($\chi^2 = 252.41$, $P < 0.001$), 4 times more likely to have sleep disturbance ($\chi^2 = 1,094.91$, $P < 0.001$), and 3 times more likely to be diagnosed

with a mental health disorder ($\chi^2 = 3,273.76$, $P < 0.001$). Individuals who died by suicide were more likely to be older (65+; $\chi^2 = 575.48$, $P < 0.001$) and live in areas with a lower median neighborhood income ($\chi^2 = 16.27$, $P < 0.001$). Correlations among all study variables are reported in Table 2. Notably, a significant positive correlation existed between chronic pain, sleep disorders, and suicide death, such that diagnosis of chronic pain was associated with suicide death and diagnosis of sleep disorder; diagnosis of sleep disorder was related to suicide death as well.

Path analysis revealed positive relationships between all covariates and the 2 endogenous variables, sleep disturbance and suicide death (Table 3). Adults ($B = 0.551$, standard error [SE] = 0.017, 95% confidence interval [CI] = 0.518 to 0.585, $P = 0.000$) and seniors ($B = 0.733$, SE = 0.021, 95% CI = 0.691 to 0.770, $P = 0.000$) were more likely than youths to be diagnosed with sleep disturbance; adults ($B = 0.461$, SE = 0.033, 95% CI = 0.404 to 0.543, $P = 0.000$) and seniors ($B = 0.513$, SE = 0.035, 95% CI = 0.459 to 0.605, $P = 0.000$) were also more likely than youths to die by suicide. Individuals with a mental health disorder in the past year were also more likely to have sleep disturbance ($B = 0.703$, SE = 0.009, 95% CI = 0.685 to 0.721, $P = 0.000$) and to die by suicide ($B = 0.615$, SE = 0.018, 95% CI = 0.581 to 0.648, $P = 0.000$). Finally, income had a positive relationship with sleep disturbance such that those living in higher income neighborhoods were more likely to have sleep disturbance ($B = 0.021$, SE = 0.009, 95% CI = 0.003 to 0.039, $P = 0.02$).

After accounting for the covariates (age, income, and mental health diagnoses), a significant positive relationship was found between chronic pain and future sleep disturbance (see Table 3, Figure 1); those who were diagnosed with chronic pain were more likely to develop subsequent sleep disturbance ($B = 0.385$, SE = 0.011, 95% CI = 0.363 to 0.408, $P = 0.000$). Similarly, sleep disturbance was positively associated with suicide death ($B = 0.171$, SE = 0.012, 95% CI = 0.145 to 0.193, $P = 0.000$). Finally, a significant indirect effect of chronic pain on suicide death, through sleep disturbance ($B = 0.066$, SE = 0.005, 95% CI = 0.056 to 0.075, $P = 0.000$; dashed line in Figure 1), and a nonsignificant direct effect of chronic pain on suicide death ($B = -0.001$, SE = 0.022, 95% CI = -0.043 to 0.042, $P = 0.976$; solid line in Figure 1) provided support for a fully mediated model.

DISCUSSION

Our data suggest that individuals who died by suicide were significantly more likely to have a diagnosis of chronic pain than controls. This finding is congruent with prior studies that have consistently demonstrated a strong relationship between chronic pain and suicidal ideation, attempt, and death.³⁰⁻³⁹ In their review on suicidality and pain, Tang and Crane identified 2 possible mechanisms by which physical pain may evolve into psychological pain and subsequent suicidal behavior over time: (1) helplessness and hopelessness about one's ability to cope with and about the chances of future relief from pain; and (2) the desire to escape the often intolerable experience of pain.⁴ These responses to pain may be particularly profound for patients faced with pain conditions such as psychogenic pain that do not have an identifiable cause, do not have clear/effective treatments, and/or may be stigmatized,³⁰ which can lead to increased feelings of hopelessness, pain catastrophizing, and elevated distress.^{30,40} Further, clinicians may undertreat pain conditions without a clear cause and/or

those that they attribute to psychiatric issues, which may, in turn, increase individuals' risk for suicide over time.³⁰ Clearly, optimizing chronic pain treatment for patients at risk for suicide is important and should be prioritized in clinical encounters; psychosocial interventions such as cognitive behavioral therapy (CBT) and dialectical behavior therapy, which have been found to be effective at reducing suicide risk,^{41,42} should address feelings of hopelessness and/or catastrophic beliefs for patients with chronic pain.⁴³

The present study provides evidence to support the hypothesis that disordered sleep may be another pathway by which chronic pain may lead to suicide. Findings from the current study indicate that individuals who had a diagnosis of chronic pain were significantly more likely to have a sleep disorder diagnosis and sleep disorders were significantly associated with suicide death. Further, after adjusting for covariates, sleep disturbance fully mediated the relationship between chronic pain and suicide death, underscoring the critical role that sleep likely plays in the well-documented relationship between pain and suicide. These findings support and extend previous studies that have similarly reported that sleep quality is a more important determinant of suicidal ideation and suicide attempts than pain duration, severity, or disability among populations with chronic pain conditions.^{10,14} From a biological perspective, findings from post-mortem studies suggest that individuals who died by suicide had lower brain levels of 5-hydroxytryptamine (serotonin) receptors.⁴⁴ Given that serotonin plays a role in both the regulation of sleep⁴⁵⁻⁴⁷ and nociception,^{48,49} chronic pain, sleep disturbance, and suicide may share a common underlying neuropathophysiology.¹⁰ From a psychosocial perspective, coping with chronic pain is often experienced as a constant struggle⁵⁰⁻⁵³ and equated with being "locked in a prison."⁵⁴ Thus, it is not surprising that the desire to escape this pain could precipitate suicidal behavior.⁵⁵ Restful sleep may be one of the few sources of refuge from pain and related negative cognitions; therefore, individuals with comorbid sleep disturbances for whom sleep cannot serve as a reprieve from their pain may be particularly vulnerable to suicidal behavior as a means of escape.¹⁰

Limitations

The present study has several limitations. One, study individuals had health insurance, including commercial insurance and Medicaid/Medicare, and were members of well-resourced health systems. Findings may differ for those without adequate access to care. Two, the study was limited to diagnoses coded by providers and are subject to coding errors; however, at least 2 related pain diagnoses that were 3 or more months apart were required in order to establish the chronic nature of the condition, minimizing errors in the identification of pain. These data also only allow for identifying when a diagnosis was documented by a provider and therefore do not necessarily capture when pain or sleep-related problems first occurred for the patient. Three, other than the nature of chronic pain for the patient population, we did not have data regarding patients' pain intensity, functional limitations, or response to pain treatments, which evidence suggests may play a role in suicide risk.⁴ Finally, we were not able to control for use of opioid medications in the present analyses. Prior studies have reported that drug overdose is the most common form of suicide attempt in chronic pain patients,⁵⁶ and access to lethal means increases suicide mortality rates⁵⁷; therefore, given that (1) opioids are commonly prescribed to treat pain,³⁰ (2) disordered sleep is a known side effect of opioids,^{58,59} and (3) opioid use is an independent risk factor

for suicide,⁴ future studies are needed to examine the mediating role of sleep disturbance in the relationship between chronic pain and suicide, controlling for opioid use and/or comparing the strength of these associations for matched individuals who were vs. were not taking opioid medications for their pain. However, despite these limitations, this study had a number of important strengths, including the large sample size, the case-control study design, use of medical record data (as opposed to relying on self-report, as was common in previous research), control for important confounders (eg, comorbid mental illness), and a focus on suicide death (in contrast with most prior studies, which have focused on suicidal ideation and/or attempt).

IMPLICATIONS/CONCLUSION

Though several previous studies have documented the association between sleep disturbance/insomnia and suicidal ideation among individuals with chronic pain,^{10,11,13,14} this is the first study to our knowledge to specifically examine the mediating role of sleep disturbance in the relationship between chronic pain and suicide death. Our finding that sleep disturbance fully mediated the relationship between chronic pain and suicide death, after adjusting for control variables, provides support for recent calls for clinicians to screen for both sleep disturbance and suicidal ideation in chronic pain patients¹⁰; this is particularly important when making treatment decisions involving opioids, which may further increase patients' risk for both sleep problems and suicide. Combined with validated suicide risk assessments, the PEGS (a validated, 4-item version of the Brief Pain Inventory-Short Form which assesses (1) a patient's pain on average in the past week, (2) the extent to which pain has interfered with the patient's enjoyment of life, (3) the extent to which pain has interfered with the patient's general activity, and (4) the extent to which pain has interfered with the patient's sleep.), may be a valuable screening tool with this population. The PEGS is brief (and therefore more realistically integrated into routine clinical encounters), viewed favorably by clinicians,⁶⁰ and includes an item specific to whether pain has interfered with the patient's sleep.⁶¹ Additional research is needed to inform decisions regarding which screening tools to administer, with which subgroups, and at what frequency.

Health systems should consider widespread implementation of behavioral interventions for patients with chronic pain such as CBT. Many of these interventions are well developed, efficacious, cost effective, and specifically focused on improving sleep.⁶² One recent randomized trial evaluated a CBT intervention for the treatment of comorbid insomnia and chronic pain and found significant improvements in both sleep and disability from pain.⁶³ Future research is needed to assess whether these types of interventions that target both sleep and pain reduce the incidence of suicidal ideation and attempts.

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Figure 1.

Path model with unstandardized coefficients and standard errors. Coefficients are adjusted for the influence of age, income, and mental health diagnosis. Solid line from chronic pain to suicide represents the direct effect; dashed line represents the indirect effect.

*** $P < 0.001$.

Table 1.

Basic Descriptives of Study Variables With Case/Control Comparisons

	Total <i>N</i> = 268,813 <i>n</i> (%)	Case <i>n</i> = 2,622 <i>n</i> (%)	Control <i>n</i> = 266,191 <i>n</i> (%)	χ^2
Chronic pain	30,705 (11.42)	557 (21.24)	30,148 (11.33)	252.41 ****
Sleep disorder	12,416 (4.62)	475 (18.12)	11,941 (4.49)	1,094.91 ****
Any mental health diagnosis	54,909 (20.43)	1,711 (65.26)	53,198 (19.98)	3,273.76 ****
Age (years)				
0 to 17	59,357 (22.08)	104 (3.97)	59,253 (22.26)	575.48 ****
18 to 64	175,308 (65.22)	1,968 (75.06)	173,340 (65.12)	
65+	34,148 (12.70)	550 (20.98)	33,598 (12.62)	
Median income (at/above)	132,453 (50.00)	1,189 (46.05)	131,264 (50.04)	16.27 ****

 $P < 0.0001$.

Table 2.

Correlations Among Study Variables

	Case	Chronic Pain	Sleep Disorder	Mental Health Diagnosis	Age	Median Income
Case	1.00					
Chronic pain	0.03 ****	1.00				
Sleep disorder	0.06 ****	0.12 ****	1.00			
Mental health diagnosis	0.11 ****	0.15 ****	0.19 ****	1.00		
Age	0.05 ****	0.19 ****	0.10 ****	0.12 ****	1.00	
Median income	-0.01 ****	-0.01 ****	-0.01 *	-0.04 ****	-0.04 ****	1.00

* $P < 0.05$;**** $P < 0.0001$.

Table 3.

Estimates of the Direct and Indirect Effects of Study Variables

Dependent Variable	Independent Variable	Regression Coefficient			P	Standardized Regression Coefficient
		B	SE	95% CI		β
Sleep disorder	Chronic pain	0.385	0.011	0.363, 0.408	0.000	0.112
	Adult	0.551	0.017	0.518, 0.585	0.000	0.240
	Senior	0.733	0.021	0.691, 0.770	0.000	0.224
	Income	0.021	0.009	0.003, 0.039	0.020	0.010
	Mental health diagnosis	0.703	0.009	0.685, 0.721	0.000	0.260
Suicide death	Sleep disorder	0.171	0.012	0.145, 0.193	0.000	0.171
	Chronic pain	-0.001	0.022	-0.043, 0.042	0.976	0.000
	Adult	0.461	0.033	0.404, 0.543	0.000	0.201
	Senior	0.513	0.035	0.459, 0.605	0.000	0.157
	Income	-0.024	0.016	-0.056, 0.009	0.143	-0.011
Total effect	Mental health diagnosis	0.615	0.018	0.581, 0.648	0.000	0.227
	Chronic pain → suicide death	0.065	0.022	0.022, 0.106	0.003	0.019
	Total indirect effect					
	Chronic pain → suicide death	0.066	0.005	0.056, 0.075	0.000	0.019

CI, confidence interval; SE, standard error.