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RESEARCH ARTICLE

Associations Between Reductions in Depressive Symptoms and Reductions in Pain and Anxiety Symptoms and Substance Use: Emulation of a Randomized Trial

Maria R. Khan, PhD, MPH,[1] Mary Acri, PhD,[2] Kaoon (Francois) Ban, MPH,[1] Joy D. Scheidell, PhD, MPH,[1] Elizabeth R. Stevens, PhD, MPH,[1] Prima Manandhar-Sasaki, MSc,[1] Dyanna Charles, MPH,[1] Natalie E. Chichetto, PhD, MSW,[3] Stephen Crystal, PhD,[4] Adam J. Gordon, MD, MPH,[5,6] Brandon D.L. Marshall, PhD,[7] E. Jennifer Edelman, MD, MHS,[8] Amy C. Justice, MD, PhD,[8,9,10] Scott R. Braithwaite, MD, MS,[1] Ellen C. Caniglia, ScD[11]

Introduction: Depressive symptoms are linked with pain, anxiety, and substance use. Research estimating whether a reduction in depressive symptoms is linked to subsequent reductions in pain and anxiety symptoms and substance use is limited.

Methods: Using data from the Veterans Aging Cohort Study, a multisite observational study of U.S. veterans, the authors used a target trial emulation framework to compare individuals with elevated depressive symptoms (Patient Health Questionnaire-9 score $\geq$ 10) who experienced reductions in depressive symptoms (Patient Health Questionnaire-9 score $<$ 10) with those whose symptoms persisted (Patient Health Questionnaire-9 score $\geq$ 10) at the next follow-up visit (on average, 1 year later). Using inverse probability of treatment weighting, the authors estimated ORs and 95% CIs for associations between depressive symptom reduction status and improvement on the following: anxiety symptoms, pain symptoms, unhealthy alcohol use, and use of tobacco, cannabis, cocaine, and/or illicit opioids.

Results: Reductions in depressive symptoms were associated with reductions in pain symptoms (OR=1.43, 95% CI=1.01, 2.02), anxiety symptoms (OR=2.50, 95% CI=1.63, 3.83), and illicit opioid use (OR=2.07, 95% CI=1.13, 3.81). Depressive symptom reductions were not associated with reductions in unhealthy alcohol use (OR=0.85, 95% CI=0.48, 1.52) or use of tobacco (OR=1.49, 95% CI=0.89, 2.48), cannabis (OR=1.07, 95% CI=0.63, 1.83), or cocaine (OR=1.28, 95% CI=0.73, 2.24).

From the [1]Department of Population Health, New York University Grossman School of Medicine, New York, New York; [2]Department of Child and Adolescent Psychiatry, New York University School of Medicine, New York, New York; [3]Department of Epidemiology, College of Public Health and Health Professions & College of Medicine, University of Florida, Gainesville, Florida; [4]Center for Health Services Research, Institute for Health, Rutgers University, New Brunswick, New Jersey; [5]Informatics, Decision-Enhancement, and Analytic Sciences (IDEAS) Center of Innovation, VA Salt Lake City Health Care System, Salt Lake City, Utah; [6]Program for Addiction Research, Clinical Care, Knowledge and Advocacy (PARCKA), Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah; [7]Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island; [8]Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut; [9]VA Connecticut Healthcare System, West Haven, Connecticut; [10]Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut; and [11]Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine

Address correspondence to: Maria R. Khan, PhD, MPH, Department of Population Health, New York University Grossman School of Medicine, 180 Madison Avenue, Floor 17, New York NY 10016. E-mail: maria.khan@nyulangone.org.

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Conclusions: Reducing depressive symptoms may potentially reduce pain and anxiety symptoms and illicit opioid use. Future work should determine whether reductions achieved through antidepressant medications, behavioral therapy, or other means have comparable impact.

INTRODUCTION

Depression is a common, chronic, and impairing disorder that the WHO ranks among the top causes of disability worldwide.[1−4] Among U.S. adults, past year prevalence of major depression is estimated to be approximately 8%, with nearly 1 in 5 of individuals aged 18−25 years experiencing depressive symptoms.[5] Lifetime prevalence of major depression is estimated to range from 13.2% to 20.6%.[4,6,7] The health and social consequences associated with depressive symptoms are substantial.[8,9] The total costs associated with depressive symptoms were estimated to be over $200 billion in 2010, with the overall economic burden due to this condition increasing over the past decade.[10,11]

Depressive symptoms often co-occur with pain symptoms, other psychiatric symptoms, and substance use.[12−17] Depressive symptoms co-occurring with pain symptoms are so common that the co-occurrence is referred to as the depression−pain syndrome.[12,15] Veterans have higher rates of depressive and pain symptoms owing to combat experiences.[18] Although the psychological and physical distress associated with chronic pain may lead to depressive symptoms,[19] there is also evidence that depressive symptoms may contribute to pain given that pain tolerance is decreased among those with depressive symptoms.[15,20] Among adults aged ≥18 years who meet the criteria for major depressive disorder (MDD), from one third to one half are estimated to be affected by an anxiety disorder[4,7]; these 2 conditions are known to co-occur, are treated with the same therapies, and are commonly viewed as different manifestations on a common psychiatric disorder spectrum.[21] There is also a strong relationship between depressive symptoms and substance use given that depression, similar to other psychiatric disorders, can lead to self-medication with drugs to attempt to regulate negative emotions.[22,23] It is estimated that among those with MDD, 45% have a substance use disorder.[7] A recent meta-analysis suggests that alcohol use disorder linked to MDD disproportionately affects men.[16]

Treatment guidelines suggest treating depressive symptoms and co-occurring conditions.[24] Yet, a majority (52.5%) of patients with co-occurring mental health and substance use conditions will not receive treatment for any condition.[25] There is some evidence to suggest that the gold-standard treatments for depressive symptoms, which include cognitive behavioral therapy, interpersonal psychotherapy, and pharmacological agents, also can improve pain symptoms[15] and substance use risk,[26] while also decreasing anxiety symptoms.[27] However, research on the relationship between reductions in symptoms of depression and improvements in other conditions is limited.

The purpose of this study was to emulate a hypothetical RCT—also called a target trial—to estimate the effect of reductions in symptoms of depression on improvements in indication of other conditions.[28−31] In the hypothetical RCT, improvement in depressive symptoms is the intervention that is randomly assigned, and the outcomes are changes in the severity of pain and anxiety symptoms and alcohol and drug use. The authors attempted to emulate the target trial using observational data from a sample of veterans, a population with elevated symptoms of depression, pain, anxiety, and co-occurring substance use.[17]

METHODS

Study Sample

The researchers used data from the Veterans Aging Cohort Study (VACS) of U.S. veterans recruited from 8 Veterans Health Administration centers: Atlanta; Baltimore; the Bronx; Houston; Los Angeles; Manhattan/Brooklyn; Pittsburgh; and Washington, District of Columbia. VACS is composed of approximately 3,500 veterans with HIV and 3,500 controls without HIV, frequency matched by age, race/ethnicity, sex and site of care.[32] Study enrollment began in 2002 and is ongoing. Data were derived from 6 approximately annual surveys. These surveys were administered from 2002 to 2015 in Atlanta, the Bronx, Houston, Los Angeles, and Manhattan/Brooklyn and from 2004 to 2015 in Pittsburgh; Baltimore; and Washington, District of Columbia. Surveys assess health outcomes, including depressive, anxiety, and pain symptoms and alcohol and drug use. Eligible individuals for this study include participants who were categorized as having elevated depressive symptoms on the basis of the Patient Health Questionnaire-9 (PHQ-9)

score ≥10 on at least 1 survey at baseline or follow-up. IRBs at each participating Veterans Health Administration medical center and affiliated academic institutions approved all parent study activities. The IRB of the New York University Grossman School of Medicine deemed the emulation trial analysis nonhuman subjects research given that it is a secondary data analysis using deidentified data.

The researchers used the target trial framework[29,30] to emulate a hypothetical RCT to evaluate whether reduction in self-reported depressive symptoms could lead to improvement in pain and anxiety symptoms and in resolution of substance use (e.g., alcohol, tobacco, cannabis, cocaine, and illicit opioid use). When it is not feasible to conduct a randomized trial, one can use the target trial framework to outline the key components of the hypothetical randomized trial. The study was informed by the STROBE guidelines,[33] given that the use of a reporting guideline improves the consistency and completeness of trial emulation.[34] As such, the authors considered how one could emulate a target trial using observational data considering the following STROBE components: eligibility criteria, hypothetical treatment strategies, start and end of follow-up, outcomes, causal contrasts of interest, and unbiased analysis plan. The authors estimated the association between a reduction in depressive symptoms—which may have occurred either in response to a behavioral intervention or medication or which may have occurred naturally—and subsequent improvement in pain symptoms, anxiety symptoms, and substance use. These causal inference methods mitigate selection bias and confounding bias in observational data analysis, strengthening the potential to make robust inference. If an association is detected, future work could try to determine whether reductions achieved through antidepressant medications, behavioral therapy, or other means have impact for a range of clustering conditions.

Measures

Depressive symptoms were measured using the PHQ-9, a 9-item screening instrument that assesses the frequency of experiencing depression-related problems (e.g., little interest or pleasure in doing things, feeling down) with response options rated on a 4-point scale ranging from 0 (not at all) to 3 (nearly every day[35]), with a total score ranging from 0 to 27. Meta-analyses have indicated that the PHQ-9 has high reliability and validity.[36] Following Kroenke,[37] the authors used a PHQ-9 score ≥10 to identify elevated depressive symptoms, a cut point with high predictive value for major depression (sensitivity: 88%, specificity: 85% in meta-analyses).[38] In descriptive analyses, the authors examined participant correlates of mild depressive symptoms (PHQ-9 scores=1−9) versus elevated (moderate/severe) depressive symptoms (PHQ-9 score ≥10).

In terms of co-occurring conditions, anxiety symptoms were assessed by a single survey item that asked whether the participant felt nervous or anxious in the 4 weeks before the survey and, if they had this symptom, the degree to which they were bothered on a 5-point Likert scale.[39] The authors coded a dichotomous variable indicating any endorsement of the symptom. Comparable single-item indicators assessing current anxiety symptoms (i.e., anxious or tense) have quite good sensitivity (87%) and specificity (74%) for detection of anxiety symptoms as indicated by the Beck Anxiety Inventory.[40] Pain symptoms were assessed by a single survey item from the Health Survey Short-Form 12, which assessed *During the last month, how much has pain interfered with your normal work (including work outside and inside the home)?* in which those who answered moderately or extremely were categorized as having elevated pain symptoms.[41,42] Short instruments focused on level of pain due to interference with activities have demonstrated strong test performance among active military and Veteran Administration patients.[43,44] Unhealthy alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT).[45−46] The AUDIT is a 10-item questionnaire assessing 3 domains of alcohol use: past year consumption based on frequency, quantity, and heavy or binge drinking; past year dependence symptoms, including impaired control, increased salience of drinking, and morning drinking; and consequences of use (e.g., guilt, blackouts, alcohol-related injury, and others' concern about one's use). Each item is scored from 0 to 4 for a maximum score of 40. On the basis of WHO guidelines, the authors dichotomized the AUDIT with a score ≥8 (as an indicator of unhealthy alcohol use vs 0−7). Review evidence suggests that the AUDIT yields a median reliability coefficient of 0.83, with a range of 0.75−0.97 and adequate test performance for detection of Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised alcohol abuse or dependence among male U.S. Veteran Administration patients (sensitivity: 71%, specificity: 85%). The authors examined dichotomous indicators (yes versus no) of other substance use, including current substantial tobacco use (≥10 cigarettes a day) and past-year use of cannabis; crack/cocaine; and illicit opioids, including heroin and/or prescription opioids such as Oxycontin, Vicodin, Percocet. Single-item indicators of self-reported drug use are established measures in the National Institute on Drug Abuse Risk Behavior Assessment battery, which has high levels of reliability and validity.[47] Furthermore, there is evidence to suggest that self-reported past-year drug use is a reliable and valid method to

assess drug exposure in primary care for detection of self-reported current drug use (sensitivity: 93%; specificity: 94%).[48] Participants were provided a list of substances (e.g., cocaine, marijuana) and were asked to indicate how often in the past 12 months they used the drug, with response options including have never tried, no use in the last year, less than once a month, 1−3 times a month, 1−3 times a week, 4−6 times a week, and every day. Illicit opioid use was considered to be present if either prescription opioid and/or heroin use was endorsed. Illicit opioid use assessment varied somewhat over VACS follow-up waves. In the baseline 2002, frequency of prescription opioid and heroin use was assessed with a single item, whereas in subsequent surveys, use was assessed separately. In 2003, participants were asked to report on use of prescription opioids (morphine, codeine, Vicodin, Percocet, Oxycontin) —prescription opioids were not assessed during the 2005 −2007 survey wave—and in 2009, they were asked to report on prescription painkillers (such as Oxycontin, Vicodin, Percocet). The combined indicator of illicit opioid use has been used previously in other VACS studies.[49,50]

The following covariates were considered in multivariable models: HIV status (living with HIV versus HIV negative), race (African-American versus other), education (less than high school education versus high school or greater), income (<$12,000 vs ≥$12,000), baseline condition status (AUDIT score; depressive symptoms; anxiety symptoms; pain symptoms; current smoking; and past-year cannabis, cocaine, other stimulant, and/or illicit opioid use), and time-varying covariates measured at 1 year (current anxiety symptoms; current elevated pain symptoms; past-year alcohol use; current smoking; and past-year cannabis, cocaine, other stimulant, and illicit opioid use).

Statistical Analysis

The authors performed analyses in SAS, Version 9.4. The researchers calculated frequencies of demographic, socioeconomic, psychiatric symptoms, and substance use background factors. The authors assessed bivariable relationships between background factors and level of depression symptom severity.

Among participants screening positive for symptoms indicative of elevated depression risk (t_o), the authors fit logistic regression models to estimate ORs and 95% CIs for associations between reductions in depressive symptoms and persistence (the ref) at the next visit (t_1) and subsequent changes in anxiety and pain symptoms and substance use at the visit after depression symptom reduction status (t_2). For example, among persons who first had symptoms of depression and who also screened positive for anxiety symptoms at visit 6, the authors examined the association between depression symptom reduction status at visit 7 and anxiety symptoms reduction at visit 8. Individuals who were classified as having an unknown depressive symptom reduction status at t_1 were censored in the analysis. Inverse probability weights were estimated to account for selection bias that may have resulted owing to censoring individuals with a missing value for depressive symptoms at t_1 by fitting a logistic regression model to predict missingness of depressive symptoms at t_1 conditional on HIV status; race; education and past year income; depressive symptoms; anxiety symptoms; pain symptoms; and alcohol, tobacco, and other drug use, including marijuana, crack/cocaine, other stimulants, and illicit opioids measured at t_o.[30] In primary analyses, the authors estimated inverse probability weights to control for confounding by fitting a logistic regression model to predict reductions in depressive symptoms conditional on the earlier-mentioned baseline factors and, in addition, past-year symptoms of anxiety and pain and use of alcohol; tobacco; and drug use, including marijuana, crack/cocaine, other stimulants, and illicit opioids measured at t_1 (same survey when depressive symptom reduction versus persistence was measured). In this model, assumptions are made that t_1 covariates could have contributed to depressive symptoms at t_1 and may be associated with outcomes at t_2, hence making these factors confounders of the association between depressive symptom reduction at t_1 and other conditions at t_2 (hence should be included in the model to mitigate confounding bias). In secondary analyses, the authors also ran analyses that omitted pain symptoms, anxiety symptoms, and substance use measured at the same wave that a reduction in depressive symptoms was assessed to estimate associations in which variables that potentially lie on the causal path between reduction in depressive symptoms and other conditions were omitted. In this model, assumptions are made that depressive symptoms at t_1 may affect t_1 covariates, which in turn may contribute to outcomes at t_2, hence making these factors potential mediators of the association between depressive symptom reduction at t_1 and pain symptom reduction at t_2 (hence should be omitted from the model to reduce overcontrolling). In preliminary analyses, the authors explored whether associations between reductions in depressive symptoms and reductions in indication of other conditions differed by HIV status; given that no material differences were observed, the authors did not stratify findings by HIV status.

RESULTS

Of 2,910 individuals who screened positive for elevated depressive symptoms at t_0 (i.e., baseline), 94.0% were

male, 62.0% were African American, 90.8% had received a high school education or higher, and 50.7% had an annual household income <$12,000 (Table 1). At the time of first positive screen for elevated depressive symptoms, the authors observed that 76.7% had anxiety symptoms, 68.1% had pain symptoms, 17.9% had unhealthy alcohol use, and 53.5% were current smokers. In the past year, 26.6% had used cannabis, 22.9% used cocaine, 4.8% used other stimulants, and 22.5% used illicit opioids.

Among those with elevated depressive symptoms at baseline (n=2,910), at the next survey, 133 (4.6%) had no symptoms of depression, 778 (26.7%) had mild depressive symptoms (PHQ-9=1−9), 975 (33.5%) had elevated symptoms, and 1,024 (35.2%) did not have a measure of depressive symptoms (Table 1). Persistence of elevated depressive symptoms generally did not differ by demographic and socioeconomic factors, although persistence was slightly more common among women (37.9%) than among men (33.2%). Persistence of elevated depressive symptoms was more common among those who had baseline anxiety symptoms (anxiety: 35.4%; no anxiety: 23.7%) and pain symptoms (pain: 37.0%; no pain: 25.8%) than among those without pain or anxiety symptoms. There did not appear to be a relationship between baseline substance use and persistence of elevated depressive symptoms.

Regarding elevated pain systems, in primary analyses, among patients who screened positive for both depressive and pain symptoms at baseline (t_o), depressive symptom reduction versus persistence (the ref) at t_1 was associated with reduction in pain symptoms at t_2 (AOR=1.43, 95% CI=1.01, 2.02) when controlling for anxiety symptoms, pain symptoms, and substance use measured at t_1 (Table 2). In secondary analyses, which excluded anxiety symptoms, pain symptoms, and substance use measured at t_1 from the model for the weights, the AOR was 2.06 (95% CI=1.52, 2.79) (Table 2).

Regarding anxiety symptoms, in primary analyses, depressive symptom reduction was associated with twice the odds of anxiety symptom reduction (AOR=2.50, 95% CI=1.63, 3.83) (Table 2). In secondary analyses, the AOR was 3.13 (95% CI=2.16, 4.53).

Regarding substance use, in primary analyses, depressive symptom reduction was associated with twice the odds of ceasing illicit opioid use (AOR=2.07, 95% CI=1.13, 3.81) (Table 2). In secondary analyses, the association between reductions in depressive symptoms and ceasing illicit opioid use was 1.45 (95% CI=0.85, 2.50). In primary analyses, depressive symptom reductions did not appear to be associated with reductions in unhealthy alcohol use (OR=0.85, 95% CI=0.48, 1.52) or use of tobacco (OR=1.49, 95% CI=0.89, 2.48), cannabis (OR=1.07, 95% CI=0.63, 1.83), or cocaine (OR=1.28, 95% CI=0.73, 2.24). Results did not vary markedly in secondary analyses.

DISCUSSION

Although the authors know that depressive symptoms often co-occur with pain symptoms, anxiety symptoms, and a range of substance use outcomes, research is limited estimating the effect of reducing depressive symptoms on symptoms of pain and anxiety and on substance use. This study is the first, to authors' knowledge, to apply causal inference methods to observational data to attempt to estimate how reducing depressive symptoms may influence reductions in pain symptoms, anxiety symptoms, and alcohol and drug use. The researchers observed evidence to suggest that reducing depressive symptoms may potentially reduce pain and anxiety symptoms and illicit opioid use. The results hence suggest that improvements in depressive symptoms may have collateral benefit, in particular for reductions in pain and anxiety symptoms and potentially opioid use. Depression treatment in RCTs should examine outcomes not only of depressive symptoms but also of pain symptoms and substance use to further improve our understanding of the range of benefits of treating depressive symptoms using the gold-standard study design.

These results corroborate prior research that has highlighted the strong interconnected relationship between depressive and pain symptoms.[15] Prior reviews have suggested that because pain tolerance is decreased among those with depressive symptoms, provision of antidepressants and other psychological therapies should be considered as a component of a multidisciplinary pain management plan.[15] Meta-analyses provide evidence that this is the case; cognitive behavioral therapy interventions have comparable effects on both conditions and are associated with a 62% reduction in distress and 69% reduction in pain.[51] Owing to the bidirectional nature of the relationship between depressive and pain symptoms,[15] treating both concurrently may lead to a greater improvement of the outcomes of both conditions more than if each were treated.

It is not surprising that reductions in depressive symptoms were strongly associated with reductions in anxiety symptoms, given the strong and well-established correlation between depression and anxiety; as noted, the 2 conditions are considered to lie on a common psychiatric disorder spectrum.[21] Indeed, meta-analyses have demonstrated that the same treatment works comparably for depressive and anxiety symptoms whether the

Table 1. Baseline Characteristics of Eligible Individuals, Overall and by Depressive Symptoms at the Next Survey, VACS

Baseline characteristic, *n* (%)	All individuals *n*=2,910	No depressive symptoms at next survey (PHQ-9=0) *n*=133	Mild depressive symptoms at next survey (PHQ-9=1−9) *n* = 778	Elevated depressive symptoms at next survey *n*=975 (PHQ-9≥10)	No depression measure at next survey *n*=1,024
HIV status					
Positive	1,460 (50.2)	84 (5.75)	434 (29.7)	465 (31.9)	477 (32.7)
Negative	1,450 (49.8)	49 (3.38)	344 (23.7)	510 (35.2)	547 (37.7)
Sex					
Male	2,736 (94.0)	126 (4.61)	735 (26.9)	909 (33.2)	966 (35.3)
Female	174 (5.98)	7 (4.02)	43 (24.7)	66 (37.9)	58 (33.3)
Race					
African-American	1,805 (62.0)	101 (5.60)	501 (27.8)	578 (32.0)	625 (34.6)
Other	1,105 (38.0)	32 (2.90)	277 (25.1)	397 (35.9)	399 (36.1)
Highest educational attainment					
Less than high school	228 (7.84)	13 (5.70)	57 (25.0)	82 (35.9)	76 (33.3)
High school or more	2,643 (90.8)	118 (4.46)	714 (27.0)	878 (33.2)	933 (35.3)
Missing	39 (1.34)	2 (5.13)	7 (18.0)	15 (38.5)	15 (38.5)
Annual household income					
<$12,000	1,475 (50.7)	71 (4.81)	387 (26.2)	508 (34.4)	509 (34.5)
≥12,000	1,335 (45.9)	57 (4.27)	360 (27.0)	433 (32.4)	485 (36.3)
Missing	100 (3.44)	5 (5.00)	31 (31.0)	34 (34.0)	30 (30.0)
Current (past 4 weeks) anxiety symptoms					
Yes	2,232 (76.7)	83 (3.72)	561 (25.1)	790 (35.4)	798 (35.8)
No	371 (12.8)	26 (7.01)	123 (33.2)	88 (23.7)	134 (36.1)
Missing	307 (10.6)	24 (7.82)	94 (30.6)	97 (31.6)	92 (30.0)
Current (past month) elevated pain symptoms					
Yes	1,982 (68.1)	67 (3.38)	488 (24.6)	734 (37.0)	693 (35.0)
No	887 (30.5)	62 (6.99)	280 (31.6)	229 (25.8)	316 (35.6)
Missing	41 (1.14)	4 (9.76)	10 (24.4)	12 (29.3)	15 (36.6)
Current (past year) unhealthy alcohol use					
Yes	522 (17.9)	26 (4.98)	163 (31.2)	194 (37.2)	139 (26.6)
No	1,882 (64.7)	88 (4.68)	560 (29.8)	677 (36.0)	557 (29.6)
Missing	506 (17.4)	19 (3.75)	55 (10.9)	104 (20.6)	328 (64.8)
Current smoker					
Yes	1,557 (53.5)	70 (4.50)	419 (26.9)	509 (32.7)	559 (35.9)
No	1,353 (46.5)	63 (4.66)	359 (26.5)	466 (34.4)	465 (34.4)

(*continued on next page*)

Table 1. Baseline Characteristics of Eligible Individuals, Overall and by Depressive Symptoms at the Next Survey, VACS (*continued*)

Baseline characteristic, *n* (%)	All individuals *n*=2,910	No depressive symptoms at next survey (PHQ-9=0) *n*=133	Mild depressive symptoms at next survey (PHQ-9=1–9) *n* = 778	Elevated depressive symptoms at next survey *n*=975 (PHQ-9≥10)	No depression measure at next survey *n*=1,024
Current (past year) cannabis use					
Yes	774 (26.6)	34 (4.39)	192 (24.8)	256 (33.1)	292 (37.7)
No	2,043 (70.2)	93 (4.55)	553 (27.1)	689 (33.7)	708 (34.7)
Missing	93 (3.2)	6 (6.45)	33 (35.5)	30 (32.3)	24 (25.8)
Current (past year) cocaine use					
Yes	666 (22.9)	37 (5.56)	196 (29.4)	211 (31.7)	222 (33.3)
No	2,157 (74.1)	91 (4.22)	557 (25.8)	736 (34.1)	773 (35.8)
Missing	87 (2.99)	5 (5.75)	25 (28.7)	28 (32.2)	29 (33.3)
Current (past year) illicit opioid use					
Yes	655 (22.5)	14 (2.14)	153 (23.4)	225 (34.4)	263 (41.5)
No	2,081 (71.5)	105 (5.05)	575 (27.6)	683 (32.8)	718 (34.5)
Missing	174 (5.98)	14 (8.05)	50 (28.7)	67 (38.5)	43 (24.7)

PHQ-9, Patient Health Questionnaire-9; VACS, Veterans Aging Cohort Study.

treatment is pharmacotherapy or cognitive behavioral therapy.[52]

The results suggest that reductions in depressive symptoms may contribute to reductions in some substance use outcomes, suggesting that self-medication of depressive symptoms with substance use may be reduced by treating depressive symptoms. Given the current epidemic of overdose deaths,[53] the potential for reduction in illicit opioid use with successful depressive symptom treatment represents an opportunity to use existing and widely available tools to support those with or at risk for illicit opioid use disorder. Improved diagnosis and treatment of depressive symptoms as a component of addressing substance use are in alignment with current guidelines.[54]

Findings of this study suggest that reductions in depressive symptoms may affect reductions in some opioid use. In prior studies, the authors also have observed that reductions in alcohol and opioid use are associated with reductions in pain symptoms and other substance use[55,56] and that reductions in tobacco use may be linked to reduced use of other substances.[57] The authors also have observed that reductions in anxiety symptoms are strongly linked to reductions in depressive symptoms, although not with reductions in substance use (unpublished).

Limitations

The results of this study must be interpreted in the context of a number of limitations. First, the authors did not conduct analyses to elucidate how and why depressive symptoms were reduced (e.g., through antidepressant medication or behavioral health appointments) given that these were beyond the scope of this paper, limiting interpretability. Furthermore, although VACS follow-up surveys were administered approximately annually, there is some heterogeneity in the duration of time between follow-ups. For example, the first follow-up was on average 1.2 years after baseline, although the maximum duration between baseline and the first follow-up was 2.3 years, whereas the second follow-up was on average 1.9 years after baseline, with a maximum duration between baseline and the first follow-up was 3.2 years. Hence, the duration of time between depressive symptom reduction and outcome measurement varied, and in some cases, delayed follow-up may limit the ability to infer causality. The data were insufficiently granular to permit ascertaining the temporal order of the primary exposure and covariates, meaning that the authors may not have successfully adjusted for confounding or may have included variables in models that lie in the causal pathway between depressive symptom reductions and improvements on other behavioral

Table 2. Among People With Symptoms Indicative of Major Depression (PHQ-9≥10) at t_0, Associations Between Reductions in Depressive Symptoms (PHQ-9≤9) and Persistence (PHQ-9≥10) at t_1 and Reductions in Depression-Clustering Conditions at t_2

Condition improves	Analysis	ORs (95% CIs)
Current anxiety symptoms		
	Unadjusted	3.20 (2.62, 4.52)
	Adjusted (primary)[a]	2.50 (1.63, 3.83)
	Adjusted (secondary)[b]	3.13 (2.16, 4.53)
Current elevated pain symptoms		
	Unadjusted	2.28 (1.70, 3.04)
	Adjusted (primary)[a]	1.43 (1.01, 2.02)
	Adjusted (secondary)[b]	2.06 (1.52, 2.79)
Past year unhealthy alcohol use		
	Unadjusted	0.99 (0.61, 1.60)
	Adjusted (primary)[a]	0.85 (0.48, 1.52)
	Adjusted (secondary)[b]	1.11 (0.67, 1.83)
Current smoking		
	Unadjusted	1.33 (0.88, 2.01)
	Adjusted (primary)[a]	1.49 (0.89, 2.48)
	Adjusted (secondary)[b]	1.46 (0.93, 2.29)
Past year cannabis use		
	Unadjusted	0.97 (0.60, 1.58)
	Adjusted (primary)[a]	1.07 (0.63, 1.83)
	Adjusted (secondary)[b]	1.10 (0.68, 1.77)
Past year cocaine use		
	Unadjusted	1.27 (0.79, 2.06)
	Adjusted (primary)[a]	1.28 (0.73, 2.24)
	Adjusted (secondary)[b]	1.45 (0.90, 2.34)
Past year illicit opioid use		
	Unadjusted	1.18 (0.71, 1.97)
	Adjusted (primary)[a]	2.07 (1.13, 3.81)
	Adjusted (secondary)[b]	1.45 (0.85, 2.50)

[a]Adjusted for HIV status, race, education, income, baseline conditions (AUDIT score; depressive symptoms; anxiety symptoms; moderate or severe pain symptoms; current smoking; and past-year cannabis, cocaine, other stimulant, and illicit opioid use) and time-varying covariates measured at 1 year (current anxiety symptoms; current pain symptoms; past-year alcohol use; current smoking; and past-year cannabis, cocaine, other stimulant, and illicit opioid use).
[b]Adjusted for HIV status, race, education, income, baseline conditions (AUDIT score; depressive symptoms; anxiety symptoms; moderate or severe pain symptoms; current smoking; and past-year cannabis, cocaine, other stimulant, and illicit opioid use), and time-varying covariates measured at 1 year (past-year alcohol use; cannabis; cocaine; other stimulant; and illicit opioid use, anxiety symptoms, smoking, and moderate or severe pain symptoms) excluded from the model for the weights.
AUDIT, Alcohol Use Disorders Identification Test; PHQ-9, Patient Health Questionnaire-9.

health outcomes. For example, if the authors are interested in the influence of reducing depressive symptoms on illicit opioid use and are concerned about confounding of this relationship by status of pain, it is possible that within the same follow-up survey, a person reported both reductions in depressive symptoms and reductions in pain. To estimate effects in which variables that potentially lie on the causal path between reduction in depressive symptoms and other conditions were omitted, the authors ran analyses that omitted pain, anxiety, and substance use measured at the same wave that reduction in depressive symptoms was assessed (secondary analyses). Finally, this study was limited by the potential measurement error that could arise from measuring depressive symptoms and related factors using screening tools or single-item indicators versus clinical diagnostic assessment tools and by dichotomization of depressive symptoms and other conditions that may lead to imprecision in estimates and potential misclassification. Specifically, the authors operationalized reduction in depressive symptoms as a drop to below the threshold of the PHQ-9 score <10, the commonly used cut point to indicate a minimal/mild depressive symptom level.[37] As long as someone falls below this threshold, someone who reduces 1 point is equated to someone who drops 5−6 points. Further research should

additionally consider how the percentage change from pretreatment to follow-up is correlated with changes in other conditions. An additional measurement limitation was that measurement of illicit opioid use disorder varied over time and did not explicitly assess nonmedical use of prescription illicit opioid or prescription opioid misuse. This lack of precision may have led to misclassification and potential bias in estimates of the relationship between reduction in depressive symptoms and illicit opioid use. Despite these numerous limitations, the findings suggest that there may be potential benefits to additional investments in depression screening and treatment, particularly in contexts of where pain and illicit opioid use are common. The study highlights the need for additional research to assess the reproducibility of findings and, if validated, to elucidate the mechanisms of how there may be an influence of depressive symptom treatment on pain and illicit opioid use but not on other substance use.

CONCLUSIONS

In summary, this study adds to an emerging body of research that expands the clinical implications of depressive symptom screening and treatment in the context of physical health, mental health, and other behavioral health priorities. In particular, the work especially highlights a potentially important opportunity to treat depressive symptom in populations with high levels of chronic pain and substance use, particularly relevant given the current epidemic of overdose deaths.

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CREDIT AUTHOR STATEMENT

Maria R. Khan: Conceptualization, Methodology, Writing — original draft. Mary Acri: Writing — review & editing. Kaoon (Francois) Ban: Formal analysis, Investigation, Writing — review & editing. Joy D. Scheidell: Writing — review & editing. Elizabeth R. Stevens: Writing — review & editing. Prima Manandhar-Sasaki: Investigation, Writing — review & editing. Dyanna Charles: Project administration, Writing — review & editing. Natalie E. Chichetto: Writing — review & editing. Stephen Crystal: Writing — review & editing. Adam J. Gordon: Writing — review & editing. Brandon D.L. Marshall: Writing — review & editing. Amy C. Justice: Funding acquisition, Writing — review & editing. Scott R. Braithwaite: Conceptualization, Methodology, Writing — review & editing, Supervision, Funding acquisition. Ellen C. Caniglia: Methodology, Writing — review & editing, Supervision.

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