

Suicide, opioids, chronic pain, and mental health disorders: a narrative review

Joseph V. Pergolizzi Jr.^{1,*}, Peter Magnusson^{2,3}, Jo Ann LeQuang¹, Robert Colucci^{1,4}, Frank Breve⁵, Giustino Varrassi⁶

¹NEMA Research, Inc., Naples, Florida, United States of America

²Centre for Research and Development, Region Gävleborg/Uppsala University, Gävle, Sweden

³Department of Medicine, Cardiology Research Unit, Karolinska Institutet, Stockholm, Sweden

⁴Colucci & Associates, LLC, Newtown, Connecticut, United States of America

⁵Mid Atlantic Pharma Tech Consultants, LLC

⁶Paolo Procacci Foundation, Rome, Italy

*Author for correspondence:
Email: jpergolizzi@nemaresearch.com

Received date: June 25, 2021

Accepted date: October 07, 2021

Copyright: © 2022 Pergolizzi Jr JV, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Suicide rates are on the rise in the United States as is mortality associated with opioid toxicity. According to the Centers for Disease Control and Prevention, about 7% of opioid overdose deaths are suicide, but this number may be under-reported. Many people who use opioids or have opioid use disorder, (OUD), may have "passive" intentions to commit suicide that are difficult to quantify. Further, both chronic pain and mental health disorders are prevalent in those who use opioids, and both are independently associated with suicide. It appears that suicide is associated with a trio of interlocking risk factors: opioids and opioid use disorder, chronic pain, and psychiatric illness. It is important to better understand the rising suicide rate so that appropriate efforts can be made to reduce it. While chronic pain, mental health disorders, and opioid use disorder are all associated with increased risk of suicide as individual factors, it is not known if they exert a synergistic effect that expose certain individuals to particularly elevated risks for suicidality.

Keywords: Opioid, Overdose, Pain, Psychiatric illness, Suicide

Introduction

Suicide is a major cause of death in the United States and many other developed nations and in the United States is the leading cause of death for those between the ages of 10 and 34 years [1]. Among all of the various forms of substance use disorder, opioid use disorder (OUD) has the strongest relationship to suicidality [2]. In 2017, over 40% of all suicide and overdose deaths involved opioids [2]. Drug overdose mortality increased by 137% from 2000 to 2014 [3]. Veteran age-adjusted drug overdose mortality increased 23.7% from 2010 to 2015 (19.7 to 24.4 per 100,000) and increased by 20.4% from 2015 to 2016 (24.4 to 29.3 per 100,000) [4]. Opioid overdose mortality in specific increased from 10.9 per 100,000 in 2010 to 19.5 per 100,000 in 2015 [4].

Most public health initiatives addressing the opioid crisis have been directed toward treating OUD rather than investigating the link between opioids and suicide. American life expectancy is declining, mainly because of deaths associated with drug overdose and/or suicide [5]. In the United States, life expectancy at birth has decreased by 0.2 years between 2014 and 2015; it plateaued in 2015-2016; then it decreased in 2017 by 0.1 year with current life expectancy at birth in the United States 78.6 years, 76.1 years for men and 81.1 years for women, respectively [6]. There is a clear association between OUD and suicide, but two additional factors emerge: chronic pain and mental health disorders. It appears as if there are three important and interlocking risk factors for suicidality: OUD, chronic pain, and psychiatric disorders.

Suicide is likely vastly under-reported, as it is still considered shameful by some and can be readily obscured by those who wish to camouflage their intentions. In addition to suicides, suicide attempts are prevalent among those with OUD, chronic pain, and/or mental health disorders. It is estimated that attempted suicides outnumber completed suicides by at least 10 to 1 [7,8].

Methods

This is a narrative review. In March and April 2021, the authors reviewed the PubMed database and searched "suicide opioid," including only peer-reviewed articles in English from medical journals that reported on clinical trials, randomized controlled trials, or meta-analyses. This yielded 32 items. The authors then searched "suicide chronic pain" using the same inclusion and exclusion criteria and retrieved 27 articles.

When searching for “suicide mental health,” which yielded 895 items many of which were older. This search was then limited to articles published in the past five years for 465 articles.

Further, the authors searched the bibliographies of these articles and searched Google Scholar for these same search terms. The authors also obtained relevant data on suicide from public health databases.

Results

Results could be grouped into those related to OUD, chronic pain, and mental health disorders.

Opioid use disorder (OUD)

Opioids are among the most frequently identified drugs in overdose suicides [9,10], and OUD is associated with a higher rate attempted suicide [11]. It has been estimated that 32% to 48% of the population with OUD will attempt suicide at least one time [12,13]. People who pursue treatment for OUD have a 14 times greater probability of dying by suicide than the general population [14]. For individuals who may entertain occasional thoughts of ending their lives, it has been speculated that opioids can help quell the normal revulsion surrounding suicide, in terms of finding the fear of death, pain, and finding an efficient and reliable means to die [15]. Opioids in general have a soothing effect, and the availability of fast-acting, highly potent opioids such as fentanyl, may further be perceived to reduce pain in those who seek an efficient means to commit suicide [11]. Furthermore, the availability of illicit opioids, including illicit fentanyl, combined with syringes means that illicit drug users with OUD are better equipped than the general population to commit suicide. A person with suicidal thoughts with no access to potentially lethal drugs and no ability to inject them is at a distinct disadvantage for committing suicide by opioid, while those with active intravenous OUD have such tools daily at their disposal [16]. Even those who take prescription opioids under close medical supervision have a reliable means for suicide by opioid, whether they think about it or not.

Per capita, more opioids are prescribed in the United States than any other nation, and from 1997 to 2007, the morphine milligram equivalents prescribed in the average opioid prescription increased from about 100 to 700 [17]. The relationship between higher prescribed doses of opioids and increased rates of fatal and nonfatal overdose has been established [18-21]. Compared to patients who receive 1 to 20 mg/day of opioids, patients prescribed over 100 mg/day have nearly a nine-fold increased risk of overdose with an annual overdose rate of 1.8% [20]. Increased rates of opioid overdose may have to do with the fact that patients in the United States are being prescribed higher doses of opioids than previously [19-21].

Opioid prescriptions and OUD are associated with suicide, but so is the discontinuation of opioids in a population that had previously taken them. In a study of 1,394,102 outpatients with an opioid prescription from the Veterans Health Administration database, discontinuing the opioid prescription was associated with an increased risk for overdose or suicide regardless of the length of opioid therapy although patients with longer therapy durations were at greater risk [22]. The hazard ratio for overdose or suicide in patients who had taken opioids for more than 400 days was 6.8 compared to 1.7 for those taking opioids under 30 days [22]. There is currently no particular program to address opioid cessation as a risk for suicide.

The role of polysubstance use disorder and suicidality remains to be elucidated. Many individuals who take illicit drugs take more than one drug and/or alcohol together at the same time. Familiar combinations include heroin plus cocaine (“speedball”) sometimes with alcohol, benzodiazepines and opioids, marijuana and alcohol, and combinations of multiple drugs taken opportunistically. Polysubstance abuse both elevates the risk of fatal opioid-associated respiratory depression and can complicate, if not prevent, opioid rescue by naloxone or other means. In this context, benzodiazepines deserve special mention. These agents are frequently prescribed anxiolytics and have themselves been associated with increased suicidality [23]. The Centers for Disease Control and Prevention (CDC) advised in its prescribing guidance to family practice physicians that benzodiazepines not be co-prescribed with opioids [24]. Both agents act as central nervous system depressants and this may increase the risk of drug-induced respiratory depression. Nevertheless, benzodiazepines are among the most frequently prescribed drugs in America [25], and they are often prescribed for chronic therapy which may be off-label use [26]. Benzodiazepines have been associated with suicidal ideation and completed suicide [27,28]. The combination effect of benzodiazepines and opioids for suicidality is not known.

Chronic pain

Chronic pain itself is associated with suicidality [29], and this risk may be elevated if such individuals are prescribed opioids [1]. Severe pain is more closely associated with suicide than mild or moderate pain [30]. It has been estimated that about one-third of chronic pain patients contemplate or attempt suicide [31]. In multivariate assessments, suicidal ideation was associated with head pain in specific (odds risk 1:9) and high pain summary scores (OR 2:3) [31].

Chronic pain is more prevalent in the homeless population than the general population, and it is less likely to be under control [32]. In a study of 1,287 homeless individuals in Canada, it was found that 43% reported moderate to severe chronic pain, for which 64% of that group sought medical care [33]. Of the homeless with moderate to severe pain, 38% said they sometimes used illicit drugs as analgesics [33]. Having a history of homelessness is in itself associated with suicidality [34].

An explanation as to why chronic pain is associated with suicide maintains that chronic pain involves unrelenting, unremitting, and sometimes unbearable suffering that can lead to familial disruptions, disability, social isolation, and depression, all of which make the individual increasingly despondent, hopeless, and despairing [35]. Mental health disorders, particularly depression, are often comorbid with chronic pain, but may not fully explain the link to suicidality [36].

Since physical pain is among the many risk factors for suicidal thoughts and behaviors [37], it has been speculated that suicidality may be associated with abnormal chronic pain processing [38]. This has yet to be fully described. Suicide has also been linked to a pro-inflammatory state, explained by the fact that dysregulation of the immune system has been associated with the pathophysiology of suicide [7]. An unanswered question is whether inflammation causes/contributes to suicidality or is merely an epiphenomenal event [7].

An intriguing new area of study involves peptides, which regulate a range of physiologic processes from pain to endocrine balance, and have been associated with highly complex psychological behaviors such as mating, parenting, social bonding, and self-harm [39]. It has been found that β -endorphin, a peptide that modulates pain, occurs in high levels among those who are more likely to report chronic pain [40] and be diagnosed with a psychiatric illness [41,42]. In fact, β -endorphin correlated with lifetime suicide events in a study of 37 depressed patients with suicidality ($r=0.702$, $p=0.007$) [38].

Mental health disorders

People with mental health disorders as defined by the Diagnostic and Statistical Manual have higher lifetime prevalence of suicidal ideation, suicide plans, and attempted suicide [43]. About 80% of those who attempt suicide in the United States have a prior mental health disorder, including but not limited to substance use disorders [44]. In fact, it may be argued that mental health disorders are a primary predictor of suicidal ideation, but poor mental health appears to be more closely tied to the onset of suicidal ideation, rather than attempted or completed suicide [44].

Not all mental health disorders are equally associated with suicidality. From a large database study ($n=887,859$ patients) at the Veterans Administration, multivariate analysis showed that the odds of completed suicide in people with a mental health disorder were highest among patients with panic disorder (OR 1.3, 95% CI, 1.0-1.5), generalized anxiety disorder (OR 1.3, 95% CI, 1.1-1.5), and other anxiety disorders (OR 1.3, 95% CI, 1.2-1.4) [23]. The mental disorders of social phobia, obsessive-compulsive disorder, and posttraumatic stress disorder were not statistically associated with completed suicide [23].

Mental health disorders are comorbid with chronic pain. About half of all patients in primary care reporting chronic painful conditions have depressive disorders [45]. Yet in a database analysis of two large claims databases, with data from 1997 to 2005, both incidence and prevalence of opioid use was three-fold greater among patients with depression than without. Moreover, the use of opioids by depressed patients was increasing and those with diagnosed depression were more likely to have a higher average daily dose, more days' supply per prescription, and more Schedule II opioids than other patients [45]. Since OUD is likewise associated with suicidality, the use of opioids in patients with chronic pain and depressive symptoms seems misplaced, but people suffering depressive symptoms and chronic pain report more and more severe physical symptoms than those without depressive symptoms [46]. In addition, patients with comorbid chronic pain and depression have higher rates of functional deficits [47] and more mental distress [48]. Depressed patients take more and higher doses of opioids, but it is likely they experience overwhelming degrees of suffering, distress, and impairment. Furthermore, anxiety and insomnia are prevalent in this comorbid population (depression and chronic pain), which may explain why about one-third of such patients are also prescribed benzodiazepines or other benzodiazepine receptor agonist drugs (Z-drugs) [49]. The combination of benzodiazepine/Z-drug, plus an opioid, elevates the risk for potentially fatal respiratory depression [24].

Functional imaging studies suggest a bidirectional relationship between mental health conditions and chronic pain, implying mutual neurological pathways [50]. The neuromodulators dopamine

and serotonin have been studied with respect to their role in both depression and pain [51]. Dopamine homeostasis has been implicated as playing a role in chronic pain, depression, and insomnia, such that dysregulation of the dopamine system might cause pain, depression, and insomnia [52]. So closely have depression and chronic pain been linked in some studies that it decades ago had been proposed that chronic pain be considered a muted form of depression [53].

Discussion

The term “deaths of despair” has been used to describe the unexplained recent increase in suicide among middle-aged, white, non-Hispanic men in the United States [54,55]. Older white men, facing the inevitable declines of aging, the erosion of social and economic structures on which they had depended, and the financial insecurities of impending retirement sought relief in death [54]. “Life weariness” is another term coined to describe the sense of emotional depletion and anxiety faced by chronic pain patients who see no clear way forward [56]. However, it remains to be explained why this despair and weariness should afflict older white men and not women or people of other ages and races. Furthermore, it remains to be seen the effect the COVID-19 lockdowns may have had on suicide rates, particularly in light of “deaths of despair” [57-60].

It is likely that the problem of suicide-by-opioid is much greater than currently described. The CDC describes opioid overdose deaths as suicide (intentional) or accidental (unintentional) but between these two poles lies a blurred area where suicide is perhaps neither intentional nor accidental. People with this so-called “passive intent” understand the risks of using opioids and other drugs but take them anyway. This group is not well studied, but it may be that some of them truly want to end their lives, but hesitate to take decisive action out of shame, fear, guilt, or for some other reason. People with OUD, particularly street people, may regard death as an escape from a life of struggle that may include loss of jobs, homelessness, health problems, violence, legal problems, and failed relationships; they may become ambivalent about death as they pursue opioids.

These four problems are intertwined: suicide, chronic pain, mental health disorders, and OUD. The links may involve neuronal pathways (such as chronic pain and depression) as well as other mechanisms that have yet to be elucidated. This problem deserves greater study, particularly as increases in these groups are occurring and likely will continue. And it may be difficult, if not impossible, to really tackle any one of these public health crises without considering the others.

Conclusion

Suicide rates are increasing as are deaths associated with opioid overdose. Related to these two alarming trends are the fact that chronic pain and mental health disorders are prevalent in these populations, creating a trio of factors that relate to suicide: opioids and opioid use disorder, chronic pain, and mental health conditions. About 7% of all opioid-overdose deaths are suicides, this number may be under-reported as it is difficult to know the intentions of many who die with opioid-associated respiratory depression. Indeed, the intentionality of many people who take opioids makes it difficult to view a decision to commit suicide in this population as a dichotomy; many may have a so-called “passive” intent to commit suicide. This is an important and urgent public health crisis that deserves further studies.

References

1. Bohnert AS, Ilgen MA. Understanding links among opioid use, overdose, and suicide. *New England Journal of Medicine.* 2019 Jan 3;380(1):71-9.
2. Bohnert KM, Ilgen MA, Louzon S, McCarthy JF, Katz IR. Substance use disorders and the risk of suicide mortality among men and women in the US Veterans Health Administration. *Addiction.* 2017 Jul;112(7):1193-201.
3. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in drug and opioid overdose deaths—United States, 2000–2014. *Morbidity and Mortality Weekly Report.* 2016 Jan 1;64(50 & 51):1378-82.
4. Peltzman T, Ravindran C, Schoen PM, Morley SW, Drexler K, Katz IR, et al. Brief Report: Opioid-Involved Overdose Mortality in United States Veterans. *The American Journal on Addictions.* 2020 Jul;29(4):340-4.
5. Madras BK, Connery H. Psychiatry and the opioid overdose crisis. *FOCUS, A Journal of the American Psychiatric Association.* 2019 Apr;17(2):128-33.
6. Centers for Disease Control and Prevention. National Center for Health Statistics. *Health, United States, 2018.* [Accessed April 11, 2021], Available <https://www.cdc.gov/nchs/data/hus/hus18.pdf>.
7. Brundin L, Bryleva EY, Rajamani KT. Role of inflammation in suicide: from mechanisms to treatment. *Neuropsychopharmacology.* 2017 Jan;42(1):271-83.
8. Bertolote JM, Fleischmann A, De Leo D, Phillips MR, Botega NJ, Vijayakumar L, et al. Repetition of suicide attempts: data from emergency care settings in five culturally different low- and middle-income countries participating in the WHO SUPRE-MISS Study. *Crisis.* 2010;31(4):194-201.
9. Sinyor M, Howlett A, Cheung AH, Schaffer A. Substances used in completed suicide by overdose in Toronto: an observational study of coroner's data. *The Canadian Journal of Psychiatry.* 2012 Mar;57(3):184-91.
10. Shields LB, Hunsaker DM, Hunsaker III JC, Ward MK. Toxicologic findings in suicide: a 10-year retrospective review of Kentucky medical examiner cases. *The American Journal of Forensic Medicine and Pathology.* 2006 Jun 1;27(2):106-12.
11. Anestis MD, Tull MT, Butterworth SE, Richmond JR, Houtsma C, Forbes CN, et al. The role of opioid use in distinguishing between suicidal ideation and attempts. *Suicide and Life-Threatening Behavior.* 2019 Dec;49(6):1680-92.
12. Roy A. Characteristics of opiate dependent patients who attempt suicide. *Journal of Clinical Psychiatry.* 2002 May 12;63(5):403-7.
13. Tréneau F, Darreye A, Staner L, Corrêa H, Weibel H, Khidichian F, et al. Suicidality in opioid-dependent subjects. *American Journal on Addictions.* 2008 Jan 1;17(3):187-94.
14. Wilcox HC, Conner KR, Caine ED. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies. *Drug and Alcohol Dependence.* 2004 Dec 7;76:S11-9.
15. Ribeiro JD, Witte TK, Van Orden KA, Selby EA, Gordon KH, Bender TW, et al. Fearlessness about death: the psychometric properties and construct validity of the revision to the acquired capability for suicide scale. *Psychological Assessment.* 2014 Mar;26(1):115.
16. Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *The Clinical Journal of Pain.* 2008 Jul 1;24(6):479-96.
17. Paulozzi LJ, Weisler RH, Patkar AA. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *The Journal of Clinical Psychiatry.* 2011;72(5):589-592.
18. Ilgen MA, Bohnert AS, Ganoczy D, Bair MJ, McCarthy JF, Blow FC. Opioid dose and risk of suicide. *Pain.* 2016 May;157(5):1079.
19. Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA.* 2011 Apr 6;305(13):1315-21.
20. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of Internal Medicine.* 2010 Jan 19;152(2):85-92.
21. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Archives of Internal Medicine.* 2011 Apr 11;171(7):686-91.
22. Oliva EM, Bowe T, Manhapra A, Kertesz S, Hah JM, Henderson P, et al. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation. *BMJ.* 2020 Mar 4;368.
23. Pfeiffer PN, Ganoczy D, Ilgen M, Zivin K, Valenstein M. Comorbid anxiety as a suicide risk factor among depressed veterans. *Depression and Anxiety.* 2009 Aug;26(8):752-7.
24. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA.* 2016 Apr 19;315(15):1624-45.
25. Agarwal SD, Landon BE. Patterns in outpatient benzodiazepine prescribing in the United States. *JAMA Network Open.* 2019 Jan 4;2(1):e187399.
26. Pergolizzi Jr JV, LeQuang JA, Raffa RB. Benzodiazepines: Thinking outside the black box. *Journal of Clinical Pharmacy and Therapeutics.* 2021 Jun 1.
27. Dodds TJ. Prescribed benzodiazepines and suicide risk: a review of the literature. *The Primary Care Companion for CNS Disorders.* 2017 Mar 2;19(2).
28. Ghosh T, Bol K, Butler M, Gabella B, Kingcade A, Kaplan G, et al. Epidemiologic assessment of benzodiazepine exposure among suicide deaths in Colorado, 2015–2017. *BMC Public Health.* 2020 Dec;20(1):1-6.
29. Elman I, Borsook D, Volkow ND. Pain and suicidality: insights from reward and addiction neuroscience. *Progress in Neurobiology.* 2013 Oct 1;109:1-27.
30. Ilgen MA, Zivin K, Austin KL, Bohnert AS, Czyz EK, Valenstein M, et al. Severe pain predicts greater likelihood of subsequent suicide. *Suicide and Life-Threatening Behavior.* 2010 Dec;40(6):597-608.
31. Ilgen MA, Zivin K, McCammon RJ, Valenstein M. Pain and suicidal thoughts, plans and attempts in the United States. *General Hospital Psychiatry.* 2008 Nov 1;30(6):521-7.
32. Fisher R, Ewing J, Garrett A, Harrison EK, Lwin KK, Wheeler DW. The nature and prevalence of chronic pain in homeless persons: an observational study. *F1000Research.* 2013;2.
33. Vogel M, Frank A, Choi F, Strehlau V, Nikoo N, Nikoo M, et al. Chronic pain among homeless persons with mental illness. *Pain Medicine.* 2017 Dec 1;18(12):2280-8.
34. Tsai J, Cao X. Association between suicide attempts and homelessness in a population-based sample of US veterans and non-veterans. *J Epidemiol Community Health.* 2019 Apr 1;73(4):346-52.

35. Dees MK, Vernooy-Dassen MJ, Dekkers WJ, Vissers KC, Van Weel C. 'Unbearable suffering': a qualitative study on the perspectives of patients who request assistance in dying. *Journal of Medical Ethics*. 2011 Dec 1;37(12):727-34.
36. Ilgen MA, Kleinberg F, Ignacio RV, Bohnert AS, Valenstein M, McCarthy JF, et al. Noncancer pain conditions and risk of suicide. *JAMA Psychiatry*. 2013 Jul 1;70(7):692-7.
37. Calati R, Bakhiyi CL, Artero S, Ilgen M, Courtet P. The impact of physical pain on suicidal thoughts and behaviors: meta-analyses. *Journal of Psychiatric Research*. 2015 Dec 1;71:16-32.
38. Kim DJ, Blossom SJ, Delgado PL, Carbajal JM, Cáceda R. Examination of pain threshold and neuropeptides in patients with acute suicide risk. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2019 Dec 20;95:109705.
39. MacDonald K, MacDonald TM. The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry*. 2010 Jan 1;18(1):1-21.
40. Bruehl S, Burns JW, Chung OY, Chont M. What do plasma beta-endorphin levels reveal about endogenous opioid analgesic function?. *European Journal of Pain*. 2012 Mar;16(3):370-80.
41. Colasanti A, Rabiner EA, Lingford-Hughes A, Nutt DJ. Opioids and anxiety. *Journal of Psychopharmacology*. 2011 Nov;25(11):1415-33.
42. Merenlender-Wagner A, Dikshtein Y, Yadid G. The β-endorphin role in stress-related psychiatric disorders. *Current Drug Targets*. 2009 Nov 1;10(11):1096-108.
43. Nock MK, Green JG, Hwang I, McLaughlin KA, Sampson NA, Zaslavsky AM, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*. 2013 Mar 1;70(3):300-10.
44. Nock MK, Hwang I, Sampson NA, Kessler RC. Mental disorders, comorbidity and suicidal behavior: results from the National Comorbidity Survey Replication. *Molecular Psychiatry*. 2010 Aug;15(8):868-76.
45. Braden JB, Sullivan MD, Ray GT, Saunders K, Merrill J, Silverberg MJ, et al. Trends in long-term opioid therapy for noncancer pain among persons with a history of depression. *General Hospital Psychiatry*. 2009 Nov 1;31(6):564-70.
46. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *General Hospital Psychiatry*. 2007 Mar 1;29(2):147-55.
47. Katon W. The effect of major depression on chronic medical illness. In: *Seminars in Clinical Neuropsychiatry* 1998 Apr; 3(2):82-86.
48. Braden JB, Zhang L, Zimmerman FJ, Sullivan MD. Employment outcomes of persons with a mental disorder and comorbid chronic pain. *Psychiatric Services*. 2008 Aug;59(8):878-85.
49. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. *Journal of General Internal Medicine*. 2002 Mar;17(3):173-9.
50. Hooten WM. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. In: *Mayo Clinic Proceedings* 2016 Jul 1; 91(7):955-970.
51. Han C, Pae CU. Pain and depression: a neurobiological perspective of their relationship. *Psychiatry Investigation*. 2015 Jan;12(1):1.
52. Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. *Sleep Medicine Reviews*. 2013 Jun 1;17(3):173-83.
53. Blumer D, Heilbronn M. Chronic pain as a variant of depressive disease: the pain-prone disorder. *The Journal of Nervous and Mental Disease*. 1982 Jul 1;170(7):381-406.
54. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *Proc Natl Acad Sci USA*. 2015;112(49):15078-15083.
55. Case A, Deaton A. Mortality and morbidity in the 21st century. *Brookings Papers on Economic Activity*. 2017;2017:397.
56. Newton-John TR. Negotiating the maze: risk factors for suicidal behavior in chronic pain patients. *Current Pain and Headache Reports*. 2014 Sep 1;18(9):447.
57. Appleby L. What has been the effect of covid-19 on suicide rates? *BMJ*. 2021 Mar 29;372.
58. Banerjee D, Kosagisharaf JR, Rao TS. 'The dual pandemic' of suicide and COVID-19: A biopsychosocial narrative of risks and prevention. *Psychiatry Research*. 2020 Nov 18;113577.
59. Faust JS, Shah SB, Du C, Li SX, Lin Z, Krumholz HM. Suicide deaths during the COVID-19 stay-at-home advisory in Massachusetts, March to May 2020. *JAMA Network Open*. 2021 Jan 4;4(1):e2034273.
60. Monteith LL, Holliday R, Brown TL, Brenner LA, Mohatt NV. Preventing suicide in rural communities during the COVID-19 pandemic. *The Journal of Rural Health*. 2020 Apr 13.