

Pain and Suicide

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Background: This paper integrates literature on non-cancer chronic pain in terms of prevalence and risk factors for suicide.

Results: The risk of death by suicide was two-fold higher in patients with chronic pain. The lifetime prevalence of suicidal ideation was between 5-32% in individuals with chronic pain, and the prevalence of suicide attempt was 2-6%. Risk factors that were identified for suicidal tendency in chronic pain included type of pain (i.e. migraine), socio-demographic factors (i.e. unemployment), pain variables, depression, sleep quality, and pain catastrophizing.

Conclusions: There is a need for increased awareness of suicide risk as well as risk factors in individuals with chronic pain. Future research in this area, such as suicide prevention programs targeting specific risk factors, should consider the large numbers of individuals at elevated risk of suicide due to pain.

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Key Words:
pain, suicide

Introduction

Suicide is the 11th most common cause of death in Taiwan, with a mortality rate of 15.2 per 100000 in 2014. Much work has focused on the association between psychiatric disorders and suicide, and efforts have been made to find other potentially vulnerable groups. Chronic pain, afflicting up to 29-40% of the population in different countries, is also a common health problem. As many researches have been done since the 1990s, newer studies have proposed an association between pain and suicidality. In the recent meta-analysis of Calati et al.[1], the odds ratios (OR) of lifetime death wish, suicide ideation (SI), suicide plan (SP), and suicide attempt (SA) were 1.50, 2.01, 2.17,

and 2.15, respectively, in adults suffering from physical pain compared to those without. This current review focuses on the progress in this field.

Results

Prevalence

Increased rates of SI are reported in people with chronic pain. The prevalence of SI among out-patients with chronic pain ranges from 5% to 32% [2-4], consistent with previous investigations [5]. As regards the prevalence of SA in patients with chronic pain, the one-year and lifetime prevalences are 2% and 6%, respectively, in the pain out-patient clinic [4]. In a nationally representative sample of American adults

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followed-up for 12 months, a similar percentage was shown: SA ranged from 1% to 2.3% in different pain conditions[6]. A population-based prospective study has a two-year cumulative occurrence of SA in headache patients of up to 8.7-9.9%[7].

Although data on completed suicide are scarce, an earlier longitudinal study in Finland reveals that those with back pain are nine times more likely to commit suicide[8]. Kikuchi published a population-based insurance cohort study in males that was started in 1994. During 1995-2001 period, the rate of completed suicide among patients in pain was 56.7/100000 person-years. This is more than two-fold higher than the suicide rates in the general population in Japan[9].

As to suicide completion method, studies show that the choice of a non-violent method (e.g., hanging and poisoning) is common in both men and women, in contrast to the known preference of men for violent methods[10]. However, Ilgen et al. report that most suicide deaths involve the use of a firearm (67.9%) among patients from the Veterans Health Administration, while poisoning is the second most common method (16.6%). This may be due to the easier access to firearms by veterans and the male majority in the study sample[6].

Risk Factors

1. Pain Type

Evidence suggests that different types of pain may affect the risk of suicide. For instance, migraine, back pain, and psychogenic pain are more predictive of suicidality compared to arthritis or tension headache, after controlling for psychiatric disorders[6]. Different gradations of risk have been clearly demonstrated by Ilgen et al. through a comparison of different types of pain and suicidal tendency. Headache has the strongest

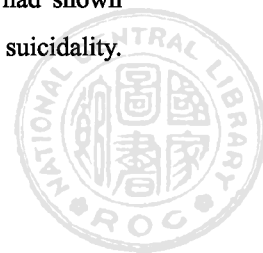
association, as patients suffering from chronic headaches are 4.3 times more likely than controls to think about suicide. It is followed by non-arthritic chronic pain (2.5 times) and back or neck pain (1.7times)[11].

Elevated suicide risk is consistently observed for migraine, with a hazard ratio of 1.34-1.7 after controlling for age, sex, and psychiatric co-morbidities, as reported in previous studies[12]. In a non-referred sample consisting of 3963 middle school students in Taiwan, migraine with aura demonstrated a higher frequency of suicide ideation (OR: 4.6, 95% confidence interval (CI): 3.0-7.0)[13]. A strong association between migraine and depression was thought to be the link.

Although longitudinal studies support a bidirectional relationship between migraine and depression, with each disorder increasing the risk of the other[14], the risk of suicide in migraine can be greatly, but not solely, explained by depression. In a nationally representative cohort in Canada (n=36984, response rate 77%), migraine is most highly associated with suicide attempt after one year of follow-up, even after adjusting for mental disorders[3], with a crude OR of 3.65 and an adjusted OR of 2.10 (95% CI: 1.29~3.42).

One of the proposed mechanisms is shared serotonergic dysfunction between migraine and suicide. Plasma serotonin level is increased during migraine attacks and decreased between migraine attacks. Reduced central serotonin is associated with suicide in cerebrospinal fluid (CSF), neurochemical, and receptor studies[15]. Moreover, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is noted in both suicide and migraine[16].

Compared to the evidence in migraine, although back pain is quite prevalent, fewer studies had shown the relationship between back pain and suicidality.



Penttinen reported significantly increased risk in committing suicide in a postal survey follow up study of 4199 Finnish farmers, relative risk was 9.1 (CI: 1.2-66)[8]. In a large nested case-control study from a primary care cohort covering 10.6 million patient records, 2306 cases of self-harm was identified and self-harm was found significantly associated to back pain after adjusted to depression, OR 1.73 (95% CI:1.20-2.47)[17]. A clinical study investigated 427 back pain patients in a tertiary pain clinic also revealed a higher prevalence of lifetime suicide risk ($\chi^2=10.43$; $p<0.01$)[18]. The scarce of evidence relating back pain and suicide is partly because of difficulty in predicting a relative rare event (suicide) when predictors are very common in the population. Besides, back pain is heterogeneous and affects patients with wide range of severity. Improved measurement of back pain severity or measure of impairment due to the pain may help to identify suicidality in this group.

Results are more discordant if more types of chronic pain lead to higher risk of suicidality. In a retrospective study, a dose-response relationship was not found between the number of pain conditions and suicide risk[6]. On the other hand, a study of 1318 patients with migraine in Taiwan reported increased odds ratio of suicide ideation and planning if co-morbid with fibromyalgia (OR: 2.61 and 1.99, respectively)[19]. In the United States, the presence of multiple pain conditions contributed to higher risk of suicide attempt in a nationally representative cohort sample. The OR increased from 0.3 to 0.7, 1.6, and 5.8, respectively, when the number of chronic pain increased from 0 to 3[11].

2. Sociodemographic Characteristics

Unemployed chronic pain patients or those on temporary or permanent disability leave are six times

more likely to report suicide ideation[4]. This is consistent with findings of a study in patients with fibromyalgia, where 50% of those who attempted suicide are unemployed. Worker's compensation status and litigation status are also predictive of suicidality in Fishbain's prospective study[20]. Lower education and female sex have been associated with the presence or degree of suicide ideation, but such findings are inconsistent, as shown in other studies.

3. Pain Variables

Contradictory results are reported by previous studies in terms of pain predictors. Hinkly et al. analyzed subgroups of five pain duration categories and reported longer pain duration involved with a greater likelihood of current suicide ideation.

High pain intensity is also proposed to contribute to suicidal ideation independent of depression severity in a study of 185 Korean patients with migraine, when depression and sociodemographic factors are controlled[21]. In a cohort comparing headaches of different kinds but of comparable magnitude, a similar elevated risk of suicide attempt related to headache intensity is noted. However, pain duration and severity are not sturdy predictors of suicidal ideation after controlling for depression[2].

4. Depression

Depression is one of the most robust correlates of suicidality in most suicide researches. Symptoms of depression are also of central importance related to the presence and severity of suicidal ideation in the pain population[22]. There is high co-morbidity between depression and pain, as the prevalence of major depression in patients with chronic pain ranges from 18% in population-based settings to 52% in pain clinics. In fibromyalgia, the lifetime prevalence of major depressive disorder even reaches 62-86%[23]. This is

not surprising since depression and chronic pain show mutual predisposition and share genetic and phenotypic qualities. Immune mechanisms, overlapping features from brain imaging studies, and changes in blood flow and neurotransmitters also provide evidence of such bidirectional relationship[24].

Studies on the risk of depression on suicidality in patients with pain are consistent. In a population-based study of suicides linked to the national hospital discharge register in Finland, suicide victims in back pain groups are more often diagnosed with depression than suicide victims without back pain[10]. Within clinical samples of patients with chronic pain, Edwards et al. reported that Beck Depression Inventory scores strongly related to suicide ideation[2], while Lee et al. found a positive correlation between depressive symptoms, assessed by Hamilton Rating Scale for Depression scores, and suicide ideation in patients with complex regional pain syndrome, after controlling for baseline psychiatric symptoms.

A population-based sample has also demonstrated that mood disorder is the most significant clinical predictor of lifetime suicide ideation, with an odds ratio of 3.2[25]. Statistical adjustments for depressive symptoms attenuate the observed risk of suicide in many researches[26]. In some extreme cases, the significant associations between pain problems and suicide even disappear after adjustment for mood disorders, indicating that suicide risk can be fully accounted for by mood disorders[3, 25].

5. Sleep Quality

Several epidemiologic studies, including a longitudinal twin study, have indicated a relationship between sleep and the risk of suicide[27]. In pain groups, patients are reported to have more suicidal ideation if they have poorer sleep, regardless of pain

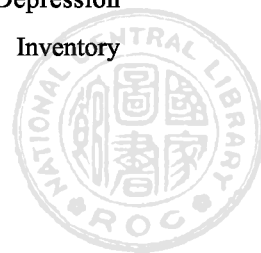
characteristics[4]. Smith et al. found a relationship between sleep onset insomnia and suicide ideation in out-patients with chronic pain[28], with poor sleep quality significantly associated with suicide attempt among patients with fibromyalgia[29].

Although sleep problems are common in depression, the relationship between sleep and suicide cannot be fully explained by depression. One meta-analysis shows that sleep quality is an important risk factor in suicide ideation, attempt, and completion, but is not mediated by depression[30]. The serotonergic raphe system may play a role, as it is involved in sleep and pain control and the 5HT-1A receptor is related to sleep deprivation-induced hypersensitivity[31]. Alterations in the serotonergic system are extensively implicated in the psychopathology of suicide behavior[32].

6. Pain Catastrophizing

Coping-related variables that incorporate elements of attention to and expansion of pain-related symptoms are of interest to investigators studying pain and suicide. Pain catastrophizing, or the giving of greater weight to the worst possible outcome, is the most consistent variable. Using the Pain Catastrophizing Scale (PCS), which consists of the rumination, magnification, and helplessness subscales, Sansone et al. demonstrated a significant relationship between pain catastrophizing and history of attempted suicide in 239 internal medicine out-patients[33]. In Racine's study, a more specific cognitive factor was identified: the PCS helplessness subscale was predictive of suicide ideation even under multiple logistic regression analyses[4].

One may argue that catastrophizing is strongly related to depressive mood. However, a study of Edwards et al. clarified this issue. Based on the evaluation of mood using the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory



(STAI), the degree of pain-related catastrophizing was a predictor of suicidal ideation after controlling for anxiety and depression[2]. Thus, catastrophizing may be a unique suicide-related cognition independent of depression.

Cognitive Inhibition as a Possible Mechanism

A complex interplay between stressors and vulnerability factors, including cognitive deficits resulting in suicidal behavior, has long been suggested. Executive functions, particularly cognitive inhibition, are more impaired in those with suicide attempts[34]. Deficits in executive control, as well as in working memory and attention, are found in pain sufferers through a performance-based test. For example, in the study by Glass[35], patients with fibromyalgia and age-matched healthy controls underwent functional magnetic resonance imaging (fMRI) in a simple Go/No-Go test. Cortical structures in the inhibition network in patients with fibromyalgia are less activated, specifically in areas related to response selection and motor preparation.

Resources may not be available for executive function, including response inhibition, when the pain processing takes place. A longitudinal study in the same group of patients with fibromyalgia further demonstrated that reduced clinical pain was associated with increased task-related brain activity in the cingulate cortex, which was involved in the response inhibition network[36].

However, patients with affective disorders also show a positive association between suicide attempt and cognitive inhibition deficit[37]. Whether less activation in the inhibition network involved in pain patients is a direct effect of pain itself or is mediated by co-morbid affective disorders, and whether this deficit precedes suicide behavior in this population, warrant further

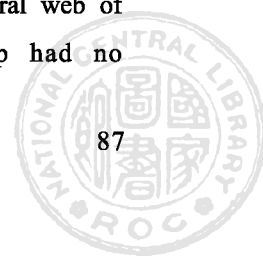
investigation.

Interventions to Decrease Suicide in Pain Patients

Studies measuring the effect of pharmacologic treatment like anti-epileptics or anti-depressants on the suicidal tendency of patients with pain are scarce. Although the antiepileptic drugs may contribute to decrease in suicidality mediated by pain relieving, FDA approved labeling, on the contrary, about an increased risk of suicidal thoughts or actions for these drugs. One pharmaco-epidemiologic study evaluated suicide rates pre- and post-gabapentin use for pain disorders[38]. This study came from the PHARMetrics Patient Centric Database, a large national database in the United States, and evaluated 107,816 pain patients treated with gabapentin. Gabapentin use had no significant effect, neither decrease nor increase, on suicide attempt (3 per 1000 person-year; 95%CI for event rate ratio: 0.78-1.26). However, the conclusion of gabapentin not reducing suicidality in pain patients can not be made from this study, since no data on whether pain was relieved by gabapentin was provided.

Pooled analysis from four double-blind, randomized, placebo-controlled clinical trials described the safety of duloxetine in patients with fibromyalgia after comparing 876 patients on duloxetine treatment and 535 patients in the placebo group[39]. There were no significant differences between duloxetine and placebo on the incidence of suicidal behavior or ideation despite of effectiveness of duloxetine on pain relieving[40] (one on duloxetine, two on placebo; $p=0.86$).

Randomized trials evaluated the efficacy of intervention to pain-related psychological distress rather than suicide. In one study, patients with migraine were divided into parallel groups, in which an experimental group was exposed to a tailored, behavioral web of intervention while the control group had no



treatment[41]. Participants in the experimental group reported significantly decreased pain catastrophizing, less depression, and increased headache self-efficacy. Another randomized controlled study involving 140 women with chronic widespread pain revealed reduced pain catastrophizing and prevention of increased symptoms and functional impairment in the treatment group, which received 4 weeks of written communication, including personalized written feedback based on cognitive behavioral principles[42]. When psychological distress is decreased by proper intervention, suicide risk may also be decreased in patients with chronic pain. However, this hypothesis warrants further evidence.

Discussion

Limitations

There are several limitations in this review that must be considered. First, studies use completed suicide rather than suicide idea or attempt as study outcomes. Second, for co-morbid conditions, instruments may not recognize sub-threshold mood symptoms and may be affected by criteria for somatic symptoms[43]. Third, pain-related disability is not well controlled in most studies and whether pain per se contributes to suicidality is unclear. Lastly, depending on the timing and severity of the pain, the extent to which pain is related to suicide varies. This cannot be fully modeled in analyses.

Conclusions

Suicide risk in chronic pain conditions is evidently prevalent. The increasing number of prospective studies, population-based cross-sectional studies, and clinical sample studies are consistent and complementary for addressing the risk of suicide in patients with chronic pain. Migraine is independently associated with

suicidality in many reports. Concordant findings have found co-morbid depression and insomnia as independent factors of suicide in the pain population, where serotonergic modulation may exert great influence. The cognitive process of pain catastrophizing and problems in cognition inhibition are other potential factors contributing to the relationship between pain and suicidality. Nonetheless, there is still a paucity of interventions for pain-related suicide. Clinicians should be cognizant of these factors and a plan of action should be developed for patients who are at high risk.

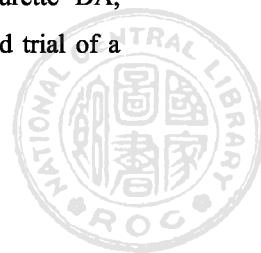
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疼痛和自殺

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背景：

本篇論文整理關於疼痛患者自殺盛行率與其危險因子的相關文獻，並予以探討。

結果：

疼痛病患自殺死亡率至少是一般人的二倍，自殺意念的終生盛行率介於5%至32%之間，而自殺企圖的盛行率則介於2至6%。慢性疼痛患者的自殺危險因子包括：疼痛種類，特別是偏頭痛、社會人口學因子如失業、疼痛相關因子、憂鬱、睡眠品質、及疼痛災難化思考等。

結論：

對於疼痛病患的自殺率及其相關危險因子應有更多瞭解。並在未來相關研究中，增加對於目前所知危險因子的預防計畫，使得因疼痛而增加的自殺危險性得以降低。

關鍵語：疼痛、自殺

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