EDITORIAL

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Chronic Pain and Suicide: Is There a Role for Ketamine?

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In the United States, the suicide rate is climbing and was reported at 13 per 100,000, the highest in 28 years.[1] Suicide is now considered as the 10th leading cause of death, and the rate has been increasing every year from 2000 to 2014 among both women and men and in every age group except those 75 and older.[1] The suicide rate among the veteran population is reportedly higher than the general population. Rates are higher for male veterans (32.1 vs. 20.9 per 100,000) than for nonveterans and much higher for female veterans (28.7 vs. 5.2 per 100,000) than for nonveterans.[2] The Veterans Health Administration (VHA) reports that the suicide rate for veterans under age 30 is also rapidly increasing and as a result the VHA declared that suicide research should be a national priority.[2] Decades of research has focused on identifying potential causes of suicide and the findings suggest that chronic pain is an important risk factor for suicidal ideation (SI), plans, and attempts.[3,4] Chronic pain with a comorbid mental health diagnosis interact to significantly increase suicidal behavior that is prevalent in the veteran population.[5] Consequently, treatment of chronic pain has been controversial because of the relationship between pain medication, substance abuse, and the risk of overdose, and these treatment risks become even more complicated when a comorbid mental health diagnosis is present. Ketamine has been identified as a possible effective treatment for cases where chronic pain, mental health diagnoses, and SI interact to create the need for addressing multiple comorbidities at once. Preliminary evidence shows that off-label use of ketamine rapidly reduces chronic pain and symptoms associated with mood disorders including suicidality with minimal side effects.

In the veteran population, chronic pain disproportionally affects those who have served or are serving in the military. More than 50% of all veterans enrolled and receiving care at the VHA are affected by chronic pain. This is a much higher rate of chronic pain than in the general adult population which is reported to be 26%.[3] One of the largest studies of the relationship between chronic pain and suicide was an analysis of 4,863,086 patients receiving care at Veteran's Affairs facilities for clinical pain and suicidal behavior. After controlling for age, sex, and medical comorbidity, the hazard ratios for death by suicide was elevated for every pain condition except arthritis and neuropathy.[5] A study that evaluated clinical cases more than 6 years showed a greater rate of completed suicide in chronic pain patients relative to the general population. Patients with psychiatric conditions and chronic pain were consistently found to be at higher risk for suicide completion than chronic pain patients who did not have any psychiatric diagnoses.[6] This data highlights the need for greater awareness of the increased risk for suicide in chronic pain patients but especially in populations that have both chronic pain and a mental health diagnosis.

Post-traumatic stress disorder (PTSD) and depression diagnoses in patients have been found to have a unique impact on suicidal behavior, especially in patients with a comorbid diagnosis of chronic pain. A large study of the veteran population found that PTSD was independently associated with significant comorbidity with mental and physical health conditions, and had independent effects on morbidity. After adjusting for sociodemographic factors, mental disorders, and severity of physical disorders, PTSD was associated with suicide attempts, and poor quality of life.[7] Depression in the veteran population is higher than the general population with 5 to 13% of veterans seen in the VHA meeting diagnostic criteria for Major depressive disorder (MDD), whereas only 3 to 5% of the general population meeting criteria for MDD.[8] Approximately 20 to 30% of suicides result from depression and high rates of depression occur in many chronic pain conditions.[8] Finding safe and effective interventions to treat patients with chronic pain that also have a comorbid diagnosis of PSTD and/or MDD could impact the overall veteran suicide rate as these diagnoses are prevalent in the veteran population and have been

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found to increase suicidal behavior. An initial randomized controlled trial conducted by Burger et al, used ketamine to treat service members with acute suicidality and depression and showed some preliminary success in reducing SI. The author concluded that ketamine could be an effective medical intervention for service members experiencing SI in the field that may need to be transported to a remote hospital for treatment.[9]

Recently, scientists have identified ketamine as a potential therapeutic option that may have rapid onset, a better side effect profile and perhaps long lasting effects which may make it ideal for acute and long-term use in suicidal patients. Ketamine has also been identified as a possible treatment for chronic pain, MDD, and PTSD as initial studies have demonstrated significant reductions in symptoms for all of these diagnoses. Ketamine is primarily an *N*-Methyl-D-aspartate receptor (NMDAR) antagonist that has been found to also be a weak μ and κ opioid receptor agonist, and an inhibitor of the reuptake of serotonin, dopamine, and norepinephrine. Ketamine has a complex pharmacology and plays a role in other cell signaling mechanisms, but the significance of these additional mechanisms in the therapeutic effects of ketamine are continuing to be explored and understood.[10] Ketamine is a racemic mixture of (S+)-ketamine and (R-)-ketamine. Some evidence from recent studies using ketamine indicate that ketamine's antidepressant effect is not caused by inhibition of the NMDAR but rather by its activation of different glutamate aminohydroxy methyl isoxazole propionic acid receptors (AMPARs). AMPARs are activated by the (R-)-ketamine metabolite called hydroxynorketamine,[11] thus it is this interaction between hydroxynorketamine and AMPARs that may be responsible for the sustained antidepressant effect. (S+)-ketamine was recently marketed as esketamine nasal spray and used in ongoing research studies because it was thought to be an easier form of drug delivery. However, this form of ketamine was shown to be less effective than ketamine given intravenously,[12] possibly because this more specific compound lacked the R enantiomer. There have also been concerns about the potential for substance abuse when esketamine is prescribed in oral or nasal spray formulations.[13]

Ketamine use at a subanesthetic dose was reviewed and found to create significant improvements in mood, anxiety, hostility, and outcomes for substance abuse treatment.[14] In multiple double-blind placebo controlled trials, intravenous infusion of ketamine was shown to be an effective intervention for Treatment Resistant Depression (TRD). The efficacy of ketamine in TRD has been proven significant in multiple double-blind placebo controlled trials.[15,16] In 2000, the first placebo controlled trial using ketamine for TRD was published and it demonstrated the rapid antidepressant effects of a single dose of ketamine but only looked at these effects for a 1-week period.[17] More recently a published investigation involving the treatment of MDD showed that ketamine in conjunction with a selective serotonin reuptake Inhibitor accelerated and enhanced the effectiveness of the selective serotonin reuptake Inhibitor in reducing depressive symptoms.[18] Based on the rapid resolution of depressive symptoms using ketamine the research community began to look at ketamine's effect on suicidality as a secondary measure. In 2011, a small preliminary observational study of patients with depression and SI presenting to the Emergency Department was published and indicated that SI in these patients was rapidly reduced following an infusion of ketamine.[19] This ED study showed that both depressive symptoms and suicidality rapidly and significantly diminished within 40 minutes with no evidence of the recurrence of symptoms 10 days postketamine administration. This preliminary study suggests that ketamine could feasibly be a safe and potentially effective medication for rapid reduction of depression and suicidality in a busy ED setting.[19] In a larger study where 133 TRD patients received a single intravenous (IV) dose of ketamine, it was noted that there were significant reductions in SI independent of depressive and anxiety symptoms.[20]

In addition to SI and depression, ketamine infusions have also been studied for the treatment of PTSD and have been shown to effectively reduce the symptoms of PTSD. In a randomized double-blind controlled trial where the effect of ketamine infusion on PTSD symptoms was examined, all three symptom clusters (intrusion, avoidance, and hyperarousal) were reduced in the group given ketamine. Additionally, ketamine showed a rapid reduction of core PTSD symptoms. The group given ketamine showed a reduction in comorbid depressive symptoms and sustained this symptom improvement 7 days postinfusion. This study also demonstrated that ketamine use in patients with chronic PTSD was generally well tolerated without significant side effects. It was noted that in the group given ketamine there were only transient dissociative symptoms without significant emergence of psychotic or manic symptoms which allays the concerns about worsening PTSD symptoms following ketamine administration.[21]

Ketamine is a well-known anesthetic with analgesic effects that can be used to treat chronic pain in a range of disorders.[14,22] There is ample evidence in the field of pain management that both oral and IV ketamine are effective treatments. Current indications for the use of oral ketamine include neuropathic pain, complex regional pain syndrome, cancer pain, orofacial pain, and phantom limb pain. The therapeutic effect of ketamine in the treatment of both depression and chronic pain is believed to be the result of antagonism of the NMDAR.[14,22] The effects of ketamine on pain, anxiety, and depression were studied in a palliative health care setting. One case from this study described a hospice patient who was treated daily with 40 mg of oral ketamine and reported relief from all three complaints. Another hospice based study administered 0.5 mg of ketamine orally over a 28-day period to hospice patients with depressive symptoms. Over half of the patients given ketamine during this trial showed significant improvement in pain and depression with few side effects.[14,22]

While patients with depression and comorbid PTSD who also experience chronic pain are known to have higher suicide rates, we speculate that effective treatment of all conditions may be associated with reductions in suicidal behavior. Until this is confirmed by future research, we believe it is imperative that providers who treat patients for chronic pain screen for suicidality and mental illness. Conversely, providers who treat patients with mental health disorders should screen patients for chronic pain and suicidality. Once these high-risk patients are identified, providers should consider multimodal therapies or pharmacotherapy with drugs that have multiple modes of action such as ketamine. In most of the preliminary research studies involving ketamine for the treatment of TRD, an IV infusion of subanesthetic low dose ketamine (e.g., 0.5 mg/kg) was used and found to rapidly reduce depression and suicidality. Ketamine delivered by infusion was shown to be well tolerated by patients and continued to have a positive impact on depression symptoms and SI for 10 days post infusion.[15] In the few chronic pain studies that examined cases of patients with TRD and chronic pain, oral dosing of ketamine was used and found to be effective for both the treatment of pain and the treatment of depression with minimal side effects.[23] The long-term effects of ketamine on the treatment of depression, PTSD, suicidality, and chronic pain need further exploration to determine the mode of delivery, long-term safety, and tolerability; however, current studies do provide reassuring data regarding short-term treatment outcomes for high-risk patients. Given the high prevalence of chronic pain, depression, and PTSD in the military population, the utilization of ketamine as a treatment option could significantly decrease the suicide rate among both veterans and active service members and improve their overall quality of life.

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