

Depression and Pain

Does Ketamine Improve the Quality of Life of Patients in Chronic Pain by Targeting Their Mood?

A LARGE population of patients concomitantly experiences chronic pain and depression or symptoms of depression (52% in pain clinics, or 85% in chronic facial pain dental clinics, for example).¹ How these two syndromes co-exist, interact, reinforce each other, and/or are maintained is poorly understood. It is not known whether pain itself can directly cause depression; if so, whether depression or its symptoms start concurrently with pain or develop while pain is perpetuated is not clear. Is it possible that the treatment of a depressive mood is sufficient to allow patients in chronic pain to return to normal activities and enjoy activities that used to make them happy? In this issue of *ANESTHESIOLOGY*, Wang *et al.* describe that acute or chronic pain (rather than stress or inflammation) causes depression-like behaviors in rats.² The authors show through pharmacologic means that the mechanisms by which pain and depression are maintained differ and are partly independent. Ketamine, in doses that did not affect evoked pain-related behaviors (10–20 mg/kg), effectively reduced depression-like behaviors (immobility using the forced swim test, and reduced sucrose preference using the sucrose preference test). Interestingly, ketamine's effects on depression-like behaviors lasted at least 5 days, far outlasting its presence in meaningful concentrations in blood or tissue. In addition, ketamine did not relieve hypersensitivity to tactile stimuli after peripheral nerve injury and yet recovered the rats' normal response to physically react to certain situations and the ability to choose a sweet solution (supposedly pleasurable) over plain water.

It seems that, at least in rodents or in the rodent model of chronic pain that the authors used, depression does not contribute to evoked peripheral nerve injury-induced pain-related behaviors. However, in humans depression can exacerbate³ or generate pain,⁴ suggesting that the treatment of depression will affect pain in patients. This discrepancy may be due to a difference between our current animal pain models and pain states in humans, or that we measure responses to evoked stimuli in rodents but measure spontaneous pain in patients. It is also possible that other types of rodent chronic pain models correlate better with clinical situations in terms of evoked pain and depression-like behaviors. Likewise, depression is the result of complex processes that are

difficult to mimic or determine in rodent models or rodent behaviors. Therefore, the return to normal behavior after ketamine under stress situations may not necessarily reflect a more proper response to such stimuli, or the preference for sucrose solution over water may not necessarily reflect the regain of pleasure for enjoyable activities. Nevertheless, these models are affected by clinically used antidepressants, and Wang *et al.* observed that these depression-like behaviors in rats were blocked by ketamine, a drug that reduces symptoms of depression in patients.⁵ This finding is indicative of the potential benefits of treating symptoms of depression in patients in pain.

This study suggests that depression or symptoms of depression (transient or chronic) are an integral part of the affective or emotional component and a consequence of acute and chronic pain conditions. One wonders to what extent the symptoms of depression contribute to the unpleasantness of pain. Is it possible that patients with chronic pain can improve their quality of life if depression is successfully treated separately? Perhaps effective treatment of depression will allow patients (still in pain) to enjoy their daily life and resume their normal activities, or allow them to perform other activities that enhance the chances to relieve their pain (physiotherapy or exercise). These intriguing conjectures seem less provocative in light of data demonstrating that patients with major depressive disorders have an altered brain processing of pain (increased emotional reactivity in pain anticipation).⁶ Is it possible that under a nondepressed state of mind patients in pain are able to cope better? Perhaps the low efficacy to effectively treat patients with chronic pain⁷ or postoperative pain⁸ will improve if clinicians take the mood of patients in chronic pain more seriously. Should we earnestly consider whether the elimination of a depressive mood has to be a concomitant strategy in the current therapies for pain? In psychiatry the standard of care in managing depression considers that a complete remission of depression is obtained only when all emotional, vegetative, and painful symptoms are treated.⁴

Chronic pain may mask depressive disorders, suggesting that we may have a larger proportion of patients with chronic pain and depressive disorders in our clinics. The benefit of including a comprehensive treatment of depression in patients with chronic pain may have additional implications

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◆ This Editorial View accompanies the following article: Wang J, Goffer Y, Xu D, Tukey DS, Shamir DB, Eberle SE, Zou AH, Blanck TJJ, Ziff EB: A single subanesthetic dose of ketamine relieves depression-like behaviors induced by neuropathic pain in rats. *ANESTHESIOLOGY* 2011; 115:812–21.

because depression is one of the most important risk factors for suicide or suicide ideation, and patients with chronic pain have higher rates of suicidal ideation.^{9,10}

This study does not rule out the possibility that the effective treatment of pain will result in an improvement of symptoms of depression. Further investigation is warranted. Certainly, in some patients antidepressants reduce both chronic pain and depression. Moreover, even though their maintenance mechanisms can differ, both pain and depression may exacerbate each other in a feedback vicious cycle in some patients, which suggests that the treatment of pain will affect depression. Ketamine seems to act differently from current antidepressants (norepinephrine and serotonin reuptake inhibitors) because ketamine acts faster as an antidepressant. In addition, ketamine reduces pain. Therefore, one can argue that ketamine may be able to prevent or disrupt more efficiently the interdependence of pain and depression.

The study of Wang *et al.* sheds light on possible improved treatments for chronic pain and sets the foundation to test whether ketamine may play a role in improving the quality of life of this patient population. They have demonstrated that low doses (subanalgesic, which minimized the appearance of undesirable side effects) can produce significant and long-lasting (at least 5 days) effects in depression-like behaviors in rats undergoing nerve injury-induced behavioral hypersensitivity. Ketamine, which may produce enduring antidepressant effects in humans,⁵ has been in clinical use for more than three decades in the United States, and more than 50 yr in Europe. Whether it is safer or more effective than traditional antidepressants for chronic therapy is unknown. Therefore,

testing of the Wang *et al.* hypothesis in patients seems an important next step.

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