Preemptive Analgesia: Is Pain Less Costly When You Pre-Pay For It?

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Issue: *Early treatment of pain could thwart the development of chronic persistent painful conditions.*

A novel treatment concept is evolving in psychopharmacology, namely, that the same treatments that can *reduce* symptoms in patients who already have a psychiatric disorder may also *prevent* symptoms in high-risk individuals who do not yet have a psychiatric disorder.[1] Thus, the mechanism whereby symptomatic suffering is relieved may also be related to the mechanism of preventing disease progression.[1] Last month we discussed how atypical antipsychotics may not only treat the symptoms of schizophrenia, but also prevent the progression of high-risk individuals to schizophrenia.[2] Here we discuss how pharmacologic agents capable of treating pain may also be useful in preventing progression to chronic persistent pain states.

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How Does Chronic Pain Evolve?

Painful experiences can imprint themselves upon the central nervous system (CNS).[3,4] For example, a chronic condition sometimes develops that produces continuous pain long after the original tissue damage from surgery.[4] Peripheral tissue injury, from sunburn to microvascular damage of peripheral nerves in painful diabetic peripheral neuropathy, can sensitize the responsiveness of the nervous system to stimuli at 2 sites, namely, peripheral and central. Peripheral sensitization reduces the threshold for pain in peripheral pain neurons.[4] Central sensitization is an activity-dependent increase in the excitability of central neurons in the spinal cord that causes an increase in the response to painful input and a decrease in the pain threshold.[3,4]

Thus, pain can beget pain. A sensitized nervous system that has experienced pain results in more pain perception than a nonsensitized nervous system. For example, circumcised boys experience more pain from subsequent vaccination than boys who are not circumcised or who were circumcised only after application of local anesthetic cream.[4] Acute pain that occurs immediately upon tissue damage sometimes is followed by modified and enduring pain responses that can outlast the tissue damage or even occur in areas without apparent tissue damage.[4]

Primary hyperalgesia is enhanced pain perception in the area of original peripheral tissue injury.[4] Secondary hyperalgesia is enhanced pain perception in undamaged tissue surrounding the area of injury. Allodynia is the misperception of non-noxious stimuli as painful. All of these can result from painful peripheral tissue damage. Functional somatic syndromes (such as fibromyalgia and irritable bowel syndrome [IBS]) are associated with painful physical symptoms in the absence of obvious peripheral tissue damage and may be linked to sensitization of central pain pathways,[3,5] as are the painful somatic symptoms that can be associated with major depressive disorder and various anxiety disorders.[6,7]

Preemptive Analgesia

The idea that you can prepay for your pain is sometimes called preemptive analgesia.[4,8–10] This treatment concept is based on the idea that chronic persistent pain states, including primary and secondary hyperalgesia, allodynia, inflammatory pain, neuropathic pain, and functional somatic syndromes, are all triggered by some combination of peripheral or

central sensitization of neurons in the pain pathway.[4,8–10] Preemptive analgesia is defined as any antinociceptive pain treatment that prevents the establishment of this altered central processing of painful input from sites of injury.[4,8–10]

The best example of preemptive analgesia is in its use for postoperative pain, in which the onset of pain can be predicted, and for which animal models have established the validity of this concept.[4] However, in clinical trials of postoperative pain, the effects of preemptive analgesia have been inconsistent, perhaps because the analgesia tested did not always fully precede, adequately block, or completely outlast the painful stimuli that accompany tissue injury from surgery.[8–10] Also, single drugs may not be as effective as multimodal pain therapies.[4] Thus, future testing of preemptive analgesia may combine anti-inflammatory agents, to block pain transduction peripherally, with regional anesthesia, to block pain transmission centrally, using central analgesics such as opiates, dual serotonin and norepinephrine reuptake blockers, and voltage sensitive calcium channel (VSCC) modulators of $\alpha_2\delta$ sites.[4,8–12]

Rescue Analgesia That Intercepts Physical Symptoms?

Persistent, unexplained, multiple painful physical symptoms are increasingly recognized as important components of major depression, anxiety disorders, and functional somatic syndromes such as fibromyalgia, IBS, and chronic back pain.[5–7] Such symptoms may have their origin within the CNS and not necessarily from peripheral tissue injury.[3] Such painful physical symptoms may also persist and be exaggerated by a central sensitization syndrome similar to the one that causes persistent pain syndromes in various inflammatory and neuropathic conditions.[3] Is it possible that the same concept of preemptive analgesia could apply to such centrally originating pain syndromes? Or, is it possible to treat multiple unexplained painful physical symptoms by rescuing them shortly after they start, and thus "intercepting" the central sensitization process before it is durably imprinted into the CNS?

It is already known that 2 agents recently proven to have efficacy for chronic neuropathic pain, namely, duloxetine and pregabalin, also have efficacy in major depression and anxiety disorders, respectively.[7,11] This effect may also apply to dual serotonin and norepinephrine reuptake inhibitors in addition to duloxetine, such as certain tricyclic antidepressants, venlafaxine, and milnacipran, as well as to $\alpha_2\delta$ ligands other than pregabalin that are also anticonvulsants and VSCC modulators, such as gabapentin. The question now is whether the long-term outcome of multiple unexplained painful physical symptoms in these psychiatric disorders without clear peripheral tissue injury can be modified by rescue analgesia. Although it is not yet possible to reliably identify individuals who are currently asymptomatic but at high risk for developing painful physical symptoms of various causes, it certainly is possible to treat patients with these symptoms as soon as such symptoms occur. Thus, major depression, anxiety disorders, and functional somatic syndromes can be treated with dual reuptake inhibitors or $\alpha_2\delta$ ligands to eliminate painful physical symptoms and improve the chances of reaching full symptomatic remission. Future testing should be done to determine whether eliminating such symptoms will improve outcomes, including preventing symptomatic relapses, the development of treatment resistance, or even hippocampal atrophy. Preemptively treating pain before it occurs, or at least rescuing the CNS from pain by intercepting pain before it becomes permanent, may be promising therapeutic applications for dual reuptake inhibitors and $\alpha_2\delta$ ligands that deserve careful clinical evaluation.

Take-Home Points

- Painful experiences can trigger 2 reactive processes in neurons of the pain pathway, one called peripheral sensitization and the other, central sensitization.
- When peripheral and central sensitization modify the responsiveness of the nervous system to pain, this imprints painful experiences upon the nervous system and hypothetically causes chronic persistent pain states.
- Preemptive analgesia aims to prevent chronic persistent pain states by administering pain medication before the development of peripheral and central sensitization.

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