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Complexities of Opioid-Induced Hyperalgesia Poorly Understood

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NATIONAL HARBOR, MD — Opioid-induced hyperalgesia is among the most pressing concerns in the national discussion of opioid addiction, underscored by the US Food and Drug Administration's (FDA) call for clinical trials to better understand the risks, but the issue is mired in more complexities and confusion than many may even realize, an expert says.

Norman Harden, MD, from the Rehabilitation Institute of Chicago at Northwestern University in Illinois, presented a very popular talk on the issue at the American Academy of Pain Medicine (AAPM) 31st Annual Meeting.

"There is a wealth of animal research showing a direct association with increased opioid use and a hyperalgesic-like phenomenon in rats, so everyone has jumped on this assumption that the same type of linear response occurs in humans," Dr Harden told the audience of pain specialists.

"But unfortunately there is limited data on whether it does translate to humans."

At the crux of the confusion is the hypersensitivity to pain that can occur in patients in chronic pain with long-term, high-dose opioid use and whether the cause is from the opioids themselves or a tolerance that has developed to the opioids — or whether the symptoms represent allodynia and hyperalgesia, the central sensitization that normally occurs in chronic pain states.

Dr Norman Harden

A look at the potential mechanisms of hyperalgesia leads to a host of possibilities, including peripheral sensitization, central sensitization, disinhibition, or possibly sympathetic nervous system involvement.

"We have to ask, is this a disinhibition process; is it peripheral sensitization and inflammation; is it all of these mechanisms, and furthermore, is it subsets of these etiologies affecting some people but not others?" Dr Harden said.

"What we do know is that it is an incredibly complicated and probably heterogeneous process that differs between individuals."

Issues of genotypes and endocrinopathy are hypothetically also parts of the puzzle as well, with some studies showing clues of hormonal changes associated with chronic pain perception, for instance.

"What we are seeing on the basis of largely uncontrolled case studies are significantly reduced levels of pregnenolone among chronic pain patients, which is at the 'top of the pyramid' of hormones," Dr Harden said.

"The lower levels of certain hormones are reportedly seen in pain patients whether they are taking opioids or not, so perhaps it is the chronic pain, and not necessarily iatrogenic causes, that is behind this endocrinopathy."

In a very preliminary effort to better understand the measures of pain to predict opioid-induced hyperalgesia, Dr Harden and his colleagues compared pain test responses among patients with chronic low back pain, including 10 who were receiving medium- to high-dose opioids (45 to 424 morphine milligram equivalency conversion) and 10 who were not taking opioids.

The study, presented at the meeting, showed no significant differences between the groups in terms of sensory tests for pain, assessed with the thermal quantitative sensory testing for warm and cold sensation and heat- and cold-induced pain, or other measures, such as thermal or mechanical wind-up or pinprick sensation.

Even more surprisingly, the one test that did show statistical significance, a pinprick wind-up test, showed a greater sensitivity not in the opioid group, as expected, but in the patients not taking opioids ($P < .03$).

"The people on opioids in fact had lower pain on this single test, and one interpretation of that would be that they're getting an analgesic effect from the opioids, not hyperalgesia," Dr Harden said. "This is 180 degrees from what we would have predicted if we had listened to and accepted (everything) about hyperalgesia in the last decade."

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Dr Harden stressed that the preliminary nature of the study should be emphasized, noting that the findings are part of what will eventually be a larger analysis.

The early findings appear to support, however, the assertion that hyperalgesia (central sensitization) in many cases may be part of the natural progression of chronic pain.

"We theorize pain drives changes in the central nervous system and that's what our research corroborates," Dr Harden said. "Maybe this is not an iatrogenic (opioid) hyperalgesia but 'natural' hyperalgesia that occurs in chronic pain."

The one certainly, however, is that much more research needs to be done concerning the hyperalgesia phenomena in order to determine, for instance, how to prevent it, Dr Harden said.

"If we're going to spend tens of millions to study hyperalgesia (as recommend by the FDA) we probably need to have a little understanding of just what it is and how it works; I can tell you we don't. We have to do a lot of work to clarify this."

Symptoms During Opioid Withdrawal

David Fishbain, MD, a professor of psychiatry and adjunct professor of neurological surgery and anaesthesiology at the University of Miami Miller School of Medicine in Florida, noted that a big factor in implicating opioid use in hyperalgesia has been observations in patient symptoms once they are tapered from the drugs.

"For years, pain centers have observed that when patients are detoxed from opioids, most of them, but not all, advise that their pain is better or same," he told *Medscape Medical News*. "This indirectly supports the concept of opioid-induced hyperalgesia."

Dr Harden agreed with the assertion. However, he pointed to an earlier uncontrolled study he conducted indicating that some patients do have a "halo effect" of resolved symptoms at first after detoxification, but that in some patients, the pain later gets worse.

Dr Fishbain agreed that much more research is necessary to better understand the phenomenon.

"There is some recent evidence that pain patients in general are hyperalgesic," he said. "This then makes it very difficult to demonstrate hyperalgesia in pain patients on opioids because you do not know what the hyperalgesia is from."

Well-designed clinical trials are needed to clarify the issue, he added.

"The issue of whether opioids induce hyperalgesia can only be settled with a prospective study where pain thresholds are measured before and after opioid treatment in humans, as has been done in rodents."

Dr Harden's study was supported by Northwestern Memorial Hospital. Dr Harden's institution has received research grants from and he has been a principal investigator for Forest Laboratories and Mallinckrodt Pharmaceuticals.

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