Does Opioid Therapy Prevent Recovery?

The new study by Per Sjøgren, MD, and colleagues suggested that long-term opioid therapy may somehow impair the ability to recover from low back and other forms of chronic noncancer pain. (See Sjøgren et al., 2010.) This is not an observation that comes out of the blue. Other researchers have made similar suggestions.

“I read the Danish study and found it completely compatible with our results,” commented James Rainville, MD, of New England Baptist Hospital in Boston in a recent e-mail. Rainville is a prominent physiatrist and researcher with a busy group practice devoted to the aggressive rehabilitation of individuals with chronic spinal problems—through the use of exercise and other therapies.

“Several years ago, we analyzed our out- come data based on the use of narcotic analgesics, and noted that none of our patients taking powerful opioids reported improvements in either pain or overall function after our rehabilitation program,” Rainville explained.

Interestingly, however, the patients taking opioids demonstrated improvements in flexibility, strength, and endurance that were similar to those of other patients in the program.

“This suggested that the benefits of exercise in desensitizing the pain-producing process may somehow have been blocked by the use of opioids,” according to Rainville.

“Interestingly, Tom Mayer, MD, and colleagues at PRIDE in Dallas noted similar results, where those on high-dose opioids reported significantly less improvement following a functional restoration program, in contrast to those not taking opioids,” Rainville said.

A 2009 study by Mayer et al. concluded that individuals on high-dose opioid therapy after work-related injuries had poorer outcomes—in terms of return-to-work, work retention, medical utilization, and long-term disability status—compared with those who did not opt for opioids. (See Kidner et al., 2009.)

“The reasons for these results are of course speculative,” said Rainville. “How- ever, they could represent interference with the adaptation of sensory neurons to therapies such as exercise or surgery. The adaptation response might be blocked by the direct biochemical impact of opioids—or could be blocked by cognitive processes, in which continuing pain is required in order to justify continuing use of opioids.

“In our practice, we no longer treat patients on high-dose opioids with rehabilitation because of the lack of response,” Rainville noted. “Instead, we require that patients first taper and discontinue opioids and then proceed with rehabilitation.

“These patients often report that their symptoms improve dramatically simply by stopping opioid use. And after dis-continuing opioids, they often make progress in pain and disability that is com- parable to those who were never on opioid therapy,” Rainville reported.

References:
A new population-based study from Denmark offers a disturbing portrait of the outcomes of medical opioid therapy for low back pain and other forms of chronic nonmalignant pain in real world settings.

Guidelines from several major professional societies have speculated that opioid therapy can provide significant pain relief, improve function, and enhance quality of life over the long term.

However, in the new study by Per Sjøgren, MD, and colleagues, this hope clashed with reality. (See Sjøgren et al., 2010.)

A previous population-based study by this research group showed that the use of medically prescribed opioids in the general population was associated with inadequate pain relief, poor quality of life, long-term unemployment, and high levels of medical care-seeking. (See Eriksen et al., 2006.)

The new study highlights further negative outcomes. It suggests that opioids might reduce the likelihood of recovery from chronic pain.

“Furthermore, the results indicated that individuals with chronic pain using strong opioids had a higher risk of death than individuals without chronic pain,” according to Sjøgren et al.

Skeptics point out that observational studies cannot prove cause and effect, and, as Sjøgren et al. acknowledged, the elevated death rate among opioid users could relate to greater severity of disease rather than opioid use.

Similarly, the poor recovery rate from chronic pain among opioid users could also reflect the magnitude of health problems rather than the opioid therapy.

“However, it is remarkable that opioid treatment of long-term/chronic non-cancer pain does not seem to fulfill any of the key opioid treatment goals: pain relief, improved quality of life, and improved functional capacity,” Sjøgren emphasized in a recent e-mail.

What About Comparisons With Other Research?

Normally, one would compare the results of observational studies with those of well-designed clinical trials to see whether the study data point in the same direction.

In this case, however, that approach is impossible. There are no long-term randomized trials of opioid therapy for chronic noncancer pain to provide guidance.

So in the absence of that comparative evidence, how seriously should health-care providers and patients take these findings?

Take the Findings Seriously?

“I would take them very seriously,” said pain researcher Dennis C. Turk, PhD, of the University of Washington in a recent e-mail. Turk is the editor-in-chief of The Clinical Journal of Pain, where the new study appeared.

“There have been a number of other studies confirming similar issues with opioids,” Turk observed.

He pointed to two ongoing cohort studies: the TROUP study and the CONSORT study. Both document disturbing trends in the prevalence and pattern of long-term opioid use. (See Campbell et al., 2010; Dunn et al., 2010; Edlund et al., 2010; and Sullivan et al., 2010.)

Turk noted that there is substantial evidence that opioids often provide less than impressive pain relief—and only in a minority of study subjects. And the pain relief may not translate into enhanced function.

“The published evidence on the efficacy of opioids, even in short-term trials, shows that the mean pain
reduction is only around 32%—and in 40% or fewer patients,” said Turk.

“Furthermore, the improvements rarely bear any relationship with improvements in physical or emotional functioning,” he added.

Turk pointed out that dropout rates from opioid trials are high even in the open-label extension of randomized controlled trials (RCTs), where more than 40% of patients discontinue therapy. And these are participants who appeared to have experienced a benefit and tolerated opioid-related side effects during the RCT phase of the study. Opioids are clearly not a miracle cure for most patients.

Do Opioids Impair Recovery?

As for opioids impairing recovery, this has been the subject of research for more than 30 years, according to Turk. There are a number of studies dating back to the 1970s providing indirect evidence that taking people off opioids in multidisciplinary pain treatment programs leads to improvements in functioning. And in some studies, a reduction in opioids also correlated with a reduction in pain.

Turk pointed out that there is also a substantial body of evidence regarding hyperalgesia or heightened pain perception after opioid therapy. In certain circumstances, chronic opioid use may lead to a paradoxical increase in pain. This could account for some of the negative outcomes with long-term opioid therapy.

A Study of Two Population-Based Health Surveys

Sjøgren and colleagues looked at data from the Danish Health Interview Survey in 2000 and then invited a subgroup of subjects back for a follow-up survey in 2005. Roughly 62% of the subjects completed the initial survey, and a similar proportion of invited subjects participated in the second survey. (See study for further details on the methodology.)

Because of the structure of the Danish healthcare system, the researchers were also able to study outcomes on an individual level via register-based outcome data.

The researchers wanted to see what proportion of the population developed chronic pain lasting more than six months—and what proportion recovered from it. They sought to identify factors that predicted chronic pain, and hoped to determine whether death rates were elevated among individuals on long-term opioid therapy.

Chronic Pain Not an Intractable Condition

On a positive note, the study showed that long-lasting chronic pain in the general population is not an intractable condition. Only a minority of subjects with chronic pain in this study had unremitting pain over long-term follow-up.

This is important information for patients with chronic pain. Many individuals with chronic pain—and their health-care providers—believe erroneously that long-standing chronic pain is an intractable and permanent condition.

The Danish study documented a substantial recovery rate. The study found that 2.7% of the population developed chronic pain annually—but that 9.4% of the chronic pain group recovered over that same time frame.

Over the study period, the cumulative six-year incidence of chronic pain development was 10.7%, and the cumulative incidence of pain recovery was 52.1%.

It is clear that people pass in and out of chronic pain states, as Sjøgren pointed out in his e-mail. “During the investigated period, 9.2% of individuals moved from a ‘no pain status’ to a ‘pain status,’ [and] 7% moved from a ‘pain status’ to a ‘no pain status,’” he reported.

So what factors predicted the development of chronic pain in this study? Increasing age up to 64 years, low educational attainment, poor self-rated health, high body mass index, and physical strain at work all predicted the development of chronic pain symptoms.

Dismal Recovery Rate for Individuals Taking Opioids

Unfortunately, however, those on chronic opioid therapy had a dismal recovery rate—even after the researchers controlled for potentially confounding factors.
“The odds for reporting recovery from chronic pain at follow-up were almost four times higher among individuals not using opioids at baseline compared with individuals using opioids,” according to the study by Sjøgren et al.

This brings up the million-dollar question. Do opioids actually impair recovery? Or does the poor recovery rate among those on long-term opioid therapy simply reflect worse health problems—and worse health trajectories?

“I think that there is a cause-and-effect relationship,” said lead author and pain specialist Sjøgren, via e-mail. “However, further validation from other research groups would be most welcome.”

“In an earlier cross-sectional study, we demonstrated that opioid usage was significantly associated with reporting of moderate, severe, or very severe pain; poor self-rated health; not being engaged in employment; higher use of the healthcare system; and a negative influence on quality of life, as registered in all items in the SF-36 questionnaire,” Sjøgren added.

Cross-sectional studies, Sjøgren observed, cannot prove causative relationships. But these trends are certainly cause for concern.

What About Risk of Death?

The study found that chronic pain was associated with a higher risk of death and that the risk was significantly higher among individuals taking strong opioids.

“The results showed that individuals with chronic pain using strong opioids had a higher risk of death than individuals without chronic pain,” according to Sjøgren and colleagues (hazard ratio, 1.67; 95% confidence interval, 1.03-2.70).

Interestingly, study subjects who took weak opioids for chronic noncancer pain did not have an elevated risk of death. The Danish researchers do not yet have access to the actual causes of death among the study subjects.

“Thus, we can only speculate that some of the long-term consequences of opioid use may be involved,” according to the study. “Addiction, opioid-induced hyperalgesia, and cognitive dysfunction may cause depressed mood and poor judgment involving suicide and hazards, and dysfunction of the immune and reproductive systems may cause increased morbidity and mortality, for example owing to infections.”

Should Patients be Informed That Opioid Therapy Might Shorten Lives?

Is there enough evidence to inform prospective patients that long-term opioid therapy might shorten their lives?

“No,” said Sjøgren, “I think it is too early to warn patients against long-term opioid treatment as more evidence is needed.

“Unfortunately, due to the latency of our death registry [i.e., the time lag between death and details about the causes of death becoming available], we cannot yet give death causes. And when we can, the registrations may be too simple and uncertain [to allow important conclusions].

“However, a number of studies on opioids show suppression of sex hormones and the immune system, which may cause premature mortality,” Sjøgren added.

“We are now following the cohort up to 2010 and will have better estimates in future publications,” Sjøgren reported.

Could the Incomplete Response To the Survey Have Biased the Study Results?

As with any survey, incomplete response can bias the results. But Sjøgren and colleagues believe that this is unlikely to have occurred.

After the 2000 survey, the researchers compared mortality rates among responders and nonresponders to the survey—and found that responders actually had a lower mortality rate than nonresponders. They also found that the elderly were more likely to be lost to follow-up than younger individuals.

“These findings were as expected and there is no indication that nonresponse has seriously biased the results of this study,” Sjøgren and colleagues concluded.
References:

Dunn KM et al., Opioid prescriptions for chronic pain and overdose: A cohort study, Annals of Internal Medicine, 2010; 152(2):85–92


