therapeutics letter
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THERAPEUTICS INITIATIVE
Independent Healthcare Evidence

Can prescribers avoid contributing to opioid use disorder?

Case vignette: *A 21 y/o has surgery for a condition expected to improve. He fills a discharge prescription for 5 days of an opioid at a standard dose. At 1-week follow-up with his family doctor for suture removal, he describes ongoing pain. Is a renewal of opioid appropriate, potentially dangerous, or both?*

Aggressive promotion of opioids for chronic non-cancer pain (CNCP) began in the 1990s, coupled with advocacy of "pain as the 5th vital sign" and popularization of numerical scales for patients to self-rate pain.[1] Enthusiasm for this approach waned as clinical experience and epidemiologic studies revealed that some patients treated for pain divert their opioid prescriptions or develop opioid use disorder (OUD). This is defined as a loss of control or compulsive use, that continues despite harmful consequences.

Unintentional deaths by opioid poisoning correlate with local dispensing. This relates partly to diversion from the intended patient, but also to delayed effects of prescription opioid use for pain. For example, in 2013, before illicit fentanyl dominated opioid overdoses, 61 of 119 British Columbians who died from overdose had not received an opioid prescription in the previous 12 months.[2] They had obtained the lethal drug(s) elsewhere.

Illicit fentanyl is now the dominant cause of opioid overdose in BC. Less than 10% of 9,964 people who experienced an opioid overdose in 2015-2016 held an active opioid prescription. However, they were more likely than matched controls to have received an opioid prescription in the previous 5 years and much more likely to have received sedative psychotropic prescription drugs.[3]

Regulators now require prescribers to document patient risks before prescribing opioids.[4-6] Although OUD is associated with substantial morbidity and mortality, most patients at potential risk will not develop it. OUD is seldom an issue for **acute pain**, which resolves with healing of tissue injury.

But for **chronic non-cancer pain**, if opioid therapy is safe for some patients, how can we identify them? Before considering that challenge, this Letter reviews what is known about the clinical effects of long-term opioid therapy in CNCP.

Does evidence support long-term opioid therapy?

The most recent systematic review for CNCP identified 96 randomized controlled trials (RCTs) with median follow-up of 60 days.[7] No trial exceeded 6 months. Opioids (buprenorphine, codeine, hydrocodone, hydromorphone, fentanyl, morphine, oxycodone, tapentadol, tramadol) produced small mean improvements in pain, physical functioning, and sleep quality. To achieve a "**minimally important (clinical) difference**", the authors estimated numbers needed to treat of about 8 for pain, 12 for physical function, 17 for sleep quality and 38 for social function.

Over time, development of pharmacological tolerance to opioids implies that even these surprisingly modest benefits may wane. But high dose opioids are not supported by valid RCT evidence.[8]

A single 12-month RCT (N=240) tested the hypothesis that an opioid strategy (compared with non-opioid drugs) would improve chronic pain and function, at the price of more frequent adverse events and worse physical and cognitive performance.[9] It randomized primary care patients with "moderate to severe" chronic back pain, or pain from osteoarthritis of the hip or knee, despite analgesic use (excluding people already taking long-term opioid therapy or with active substance use disorder). The opioid group could be titrated to an estimated morphine equivalent (ME) of 100mg/d (as morphine, oxycodone, or hydrocodone). Less than 15% of patients

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reached ME of 50mg/d, with a 12 month mean of 21mg/d. **Opioids did not improve pain-related function.** At 12 months, the non-opioid group rated pain severity numerically lower than the opioid group: difference 0.5 on a 10-point scale (95% CI 0.0-1.0). This was below the pre-defined minimal clinically important difference between groups of 1 point. For functional or pain response defined by an individual's 30% improvement from baseline, the opioid strategy was also not superior.

As for other symptomatic drug therapies, no multi-year RCTs are available to illuminate benefits or harms of long-term opioid therapy.[7,10] Thus we still lack evidence that **long-term** opioid therapy is an effective way to manage chronic non-cancer pain.

What is the evidence about harms other than OUD?

Reversible harms are well known: hypoventilation, sedation, constipation, nausea/vomiting and dry mouth. But long-term opioid therapy also appears to increase **mortality**. At a median ME dose of 50mg/d, a retrospective cohort study of Tennessee Medicaid patients estimated absolute risk increase of 0.7% per year (95% CI 0.28-1.21%, NNH=143/yr) vs. low-moderate dose anticonvulsants or tricyclic antidepressants. Over two thirds of excess deaths outside hospital attributed to opioids were not from accidental overdose, and primarily cardiovascular.[11] **There is no evidence that long-term use of codeine or tramadol is safer than more potent opioids.**[12,13]

Can we reliably identify patients at low risk before starting a prescription OUD?

Despite regulatory and guideline advice on patient screening, popular clinical strategies to identify low versus high-risk patients have not been reviewed critically. Primary care commonly applies the "Opioid Risk Tool."[14]

A 2019 systematic review of strategies to identify patients at risk of developing OUD suggests caution about applying risk estimation to clinical decisions.[15] For people with pain who are not already using opioids, all screening tools (including the "Opioid Risk Tool") are based on lower quality studies or demonstrate extremely poor diagnostic performance. A history of opioid or non-opioid substance use disorder, personality disorder, pain or somatoform disorder, psychosis, mood or anxiety disorder and concomitant use of psychotropic medications seem to increase risk of OUD. However, while absence of a mood disorder appears to somewhat reduce this risk, **prescribers still have no reliable way to identify patients for whom long-term opioid therapy can be prescribed safely.**

Conclusions

Unsafe opioid prescribing (including for codeine and tramadol) can increase the prevalence of OUD in people with pain. Anticipating and preventing this could reduce premature deaths and serious morbidity. To avoid engendering OUD, prescribers should adopt universal precautions for opioid-naïve patients and communicate important new evidence:

- Long-term opioid therapy is unlikely to benefit most people with chronic non-cancer pain.
- There is no valid tool, nor validated way to identify patients at low risk for OUD when starting opioids.
- Reserve opioids for severe acute non-cancer pain – at low doses for short courses.

Case vignette: *Renewing an opioid for the 21 y/o recovering from surgery is not advisable.*

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