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PERSPECTIVE

Opioids should not be prescribed for chronic pain after spinal cord injury

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Abstract

Most people with spinal cord injury (SCI) have chronic pain and effective treatments have not been identified. Within the first two decades of the 21st century, opioids have been commonly prescribed in an attempt to manage pain after SCI, however, the risks and absence of benefit of opioids have become more apparent as opioid crises have developed around the world. This perspective is an argument for why opioids should no longer be prescribed to treat chronic pain after SCI.

Chronic pain after spinal cord injury (SCI) is common with nearly four out of five people reporting ongoing pain of which approximately half is musculoskeletal and half is neuropathic [1, 2]. Treatment efficacy is often suboptimal as evidenced by the persistently high prevalence of pain over time [1, 2]. As a result it is not surprising that persons with SCI are both significantly more likely to be long-term users of short-acting opioids and to be more likely to be taking high doses of long-acting opioids than their propensity score-matched controls [3]. It is also likely that clinicians who treat people with SCI will encounter someone whose pain is not controlled despite being treated with all the recommended treatments supported by the best available evidence [4]. It is at this point that the treating clinician faced with a patient with seemingly uncontrolled pain and few options needs to make a decision as to whether opioids should be started if the individual is not being treated with them already or dose escalated, continued, or tapered if the individual is currently being treated with opioids.

There are at least four reasons why a clinician should not be tempted to begin or escalate opioids for the treatment of SCI related pain, either for musculoskeletal pain or for neuropathic SCI pain. Moreover, if a person is already being prescribed opioids, the clinician should slowly begin to taper the opioids off. These reasons include (1) a lack of evidence for the effectiveness of chronic opioids for decreasing pain intensity or improving quality of life; (2) the avoidance of a risk of opioid overdose causing respiratory depression and death; (3) the avoidance of adverse effects of opioids such as constipation, mental slowness, and hormonal depression; and (4) the avoidance of the risk of developing an opioid use disorder.

Lack of effectiveness

There are no randomized controlled (Level 1) studies that support the premise that opioids are effective for the treatment of pain after SCI in either the short or long term, except for one small study supporting the effectiveness of tramadol in the short term [4–7]. This lack of evidence for effectiveness in the long term is not unique to pain after SCI, as summarized in the recent United States Centers for Disease Control and Prevention Guideline for prescribing opioids for chronic pain [8].

Moreover, findings from a recent systematic review of chronic opioid dose reduction interventions suggest that individuals who taper off opioids, not uncommonly, report improvements in function without an associated worsening in pain, actual decreased pain levels, and improvements in quality of life [9]. Potential reasons for these perhaps non-intuitive outcomes related to long term opioid dose reduction or discontinuation include (1) alleviation of common opioid adverse effects that can worsen function and quality of life, such as constipation, fatigue, poor sleep, and depressed mood; (2) resolution of opioid-induced hyperalgesia; and (3) initiation of non-opioid pain management

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interventions [9]. There is also some evidence that the reluctance of many individuals on chronic opioid therapy to begin to decrease their intake of opioids may actually be related to a fear of opioid withdrawal rather than any actual benefit from the drug [10].

Risk of overdose

Opioids frequently cause physical dependence and users develop tolerance, which often leads to a gradual dose escalation of opioids as there is a perceived loss of effectiveness over time [11]. Dose escalation is a significant concern as it increases an individual's risk for fatal overdose. The odds of overdose increase as the dose per day increases. Comparisons of opioid doses administered per day between different drugs can be made simply by converting each to a common measure of morphine milligram equivalent (MME) doses per day by multiplying the daily dose of any opioid by a conversion factor (see Table 1). Persons taking between 20 and 50 MME per day of opioids have twice the odds of overdosing compared to those who take less [8]. For those taking doses between 50 and 100 MME per day the odds of overdosing increases to nearly five times while for doses of more than 100 MME/day the odds approach ten times the odds that are associated with taking less than 20 MME/day [8].

Another way of demonstrating the magnitude of overdose risk is illustrated by a recent study of persons with non-SCI non-cancer pain, where one in 32 individuals prescribed more than 200 MME per day died from an opioid related overdose [12]. Persons with cervical and

Table 1 Morphine milligram equivalent (MME) doses for commonly prescribed opioids [21]

Opioid	Conversion factor[a]
Codeine	0.15
Fentanyl transdermal (in mcg/h)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	3
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tramadol	0.1

[a]Multiply the dose for each opioid by the conversion factor to determine the dose in MMEs. For example, tablets containing hydrocodone 5 mg and acetaminophen 300 mg taken four times a day would contain a total of 20 mg of hydrocodone daily, equivalent to 20 MME daily; extended-release tablets containing oxycodone 10 mg and taken twice a day would contain a total of 20 mg of oxycodone daily, equivalent to 30 MME daily. All doses are in mg/day except for fentanyl, which is mcg/h

upper thoracic SCI have additional further risks for overdose. These include respiratory insufficiency related to the SCI, sleep disordered breathing, and polypharmacy with other respiratory depressant medications. The prevalence of sleep disordered breathing in persons with complete tetraplegia is over 50% [13] while 70% to 85% of persons taking opioids have sleep disordered breathing, of which a high proportion is moderate to severe [14]; the combination of etiologies of sleep disordered breathing likely increases the severity of the effect.

With regards to polypharmacy, one particularly dangerous combination of drug classes is that of opioids and benzodiazepines. Depending on the series cited, one to two thirds of fatal overdoses involve a combination of opioids and benzodiazepines [15, 16]; the latter not uncommonly prescribed for recalcitrant spasticity, anxiety, and sometimes insomnia in persons with SCI. Concurrent use of a benzodiazepine and an opioid increases the risk of overdose four to tenfold over opioid use alone [17, 18]. Of note, the discontinuation of opioids and benzodiazepines done separately have been shown to decrease the severity of sleep disordered breathing [14, 19].

Other adverse effects

Opioids have other adverse effects other than the respiratory depression. Opioids decrease gastrointestinal mobility, which can lead to poor bowel emptying, abdominal distension, bloating, and secondary chronic abdominal pain. Additionally, opioids significantly affect levels of endogenous hormones including luteinizing hormone, follicle-stimulating hormone, estrogen, and testosterone, which can adversely affect libido and fertility [11]. Opioids also commonly cause sedation and impaired cognition. In the previously referenced tramadol study, nearly half of subjects discontinued participation in the trial due to adverse effects [6].

Risk of opioid use disorder

Opioid use disorder (previously classified as opioid abuse) is defined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) as a problematic pattern of opioid use leading to clinically significant impairment or distress, manifested by at least two defined criteria occurring within a year [20]. The prevalence of this condition cited in the literature among patients with chronic pain on opioid therapy ranges between 3 and 26% in primary care settings and between 2 and 14% in a pain clinic settings [8]. The odds of developing an opioid use disorder has been found to correlate with the daily dose of opioid

prescribed. When compared to a person not being pre-scribed opioids, the odds of developing an opioid use dis-order increase from 15 times for a person taking less than 36 MME per day to 30 times for a person taking between 36 and 120 MME per day. The odds of developing an opioid use disorder further increases to 122 times for a person taking more than 120 MME per day [21]. This correlates with a risk of developing an opioid use disorder of 1% with lower-dose (less than 36 MME) and 6% with higher-dose (more than 120 MME) chronic opioid therapy [21].

It should be noted that there are effective treatments for opioid use disorder, specifically medication-assisted treat-ment with buprenorphine, naltrexone, or methadone main-tenance therapy in combination with behavioral therapies [8], however the current societal need outpaces the supply, at least in the United States [22].

Finally, although there are likely some individuals with SCI who have chronic pain, either neuropathic or noci-ceptive, that may respond to opioids and experience an improved quality of life, and not require escalating doses, this may not be the usual case. Prescribers in the United States seem to be starting to get this message and opioid prescribing, which peaked in 2010 with nearly 250 billion MME, was down to nearly 200 billion MME in 2016, a decrease of 20%, although still much higher than the 50 billion MME prescribed in 1992 [23]. It is interesting to note that the decrease could nearly all be accounted for by a decrease in prescription of extended release opioids.

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