Clinical Note

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Withdrawal-associated injury site pain (WISP): a descriptive case series of an opioid cessation phenomenon

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Abstract

Withdrawal pain can be a barrier to opioid cessation. Yet, little is known about old injury site pain in this context. We conducted an exploratory mixed-methods descriptive case series using a web-based survey and in-person interviews with adults recruited from pain and addiction treatment and research settings. We included individuals who self-reported a past significant injury that was healed and pain-free before the initiation of opioids, which then became temporarily painful upon opioid cessation—a phenomenon we have named withdrawal-associated injury site pain (WISP). Screening identified WISP in 47 people, of whom 34 (72%) completed the descriptive survey, including 21 who completed qualitative interviews. Recalled pain severity scores for WISP were typically high (median: 8/10; interquartile range [IQR]: 2), emotionally and physically aversive, and took approximately 2 weeks to resolve (median: 14; IQR: 24 days). Withdrawal-associated injury site pain intensity was typically slightly less than participants' original injury pain (median: 10/10; IQR: 3), and more painful than other generalized withdrawal symptoms which also lasted approximately 2 weeks (median: 13; IQR: 25 days). Fifteen surveyed participants (44%) reported returning to opioid use because of WISP in the past. Participants developed theories about the etiology of WISP, including that the pain is the brain's way of communicating a desire for opioids. This research represents the first known documentation that previously healed, and pain-free injury sites can temporarily become painful again during opioid withdrawal, an experience which may be a barrier to opioid cessation, and a contributor to opioid reinitiation.

Keywords: Pain, Substance withdrawal syndrome, Opioid, Opioid dependence, Hyperalgesia, Opioid-induced hyperalgesia, Self-report, Mixed methods

1. Introduction

A growing appreciation of the deleterious effects of short- and long-term opioid use[8,27,38,42,56,57,90,97,99,103,114,122,130] has spurred the need to address barriers to opioid cessation. Among these barriers, pain during or right after opioid withdrawal may be key.[82,107] Generalized myalgias and arthralgias are well known to occur during opioid withdrawal,[53] and were described as "*internal rheumatism*" almost 2 centuries ago.[110]

It is known that opioid use itself can cause adaptations in the central nervous system that lead to increased pain sensitivity, termed opioid-induced hyperalgesia (OIH),[3,6,10,21,32,41,65,68,84,91,92] clinically first described over a century ago.[2] Opioid-induced hyperalgesia is at times confused with tolerance, which may be distinct in both mechanism and treatment.[6,29,51] Once opioids are stopped, the pain sensitivity can continue or seem to heighten temporarily because any pain-relieving effect opioids may have provided is eliminated, and the drug-opposite effect can take time to subside.[139] Also, in preclinical models, opioid withdrawal induces central changes in neurotransmitters, along with neuroimmune and neuroinflammatory mediators involved in nociception,[43,44] thus potentially intensifying pain beyond OIH. A general increase in pain sensitivity after opioid cessation can occur after acute[4,55] or chronic[66,109,132,144] opioid exposure, referred to by a variety of names including withdrawal-induced hyperalgesia (WIH). For individuals with chronic noncancer pain (CNCP) or an opioid use disorder (OUD), severity of pain during and immediately after opioid withdrawal can be a risk factor for restarting opioids.[17,63,82,107,124] As a result, dose reduction or elimination can be difficult for those who take opioids, and can create enormous challenges in the doctor–patient relationship.[52]

Along with the above pain syndromes, we have observed patients who report that pain can reoccur at their old, previously

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healed, and previously pain-free injury sites during rapid opioid cessation, and that this reoccurring pain can resolve once the opioid withdrawal syndrome is over. To our knowledge, no previous studies have described such a pain experience.

Qualitative research can supplement quantitative results and help record new experiences, point to possible etiologies, and assist with future directions in research and treatment.[36] Therefore, we undertook an exploratory mixed-methods study to document the existence and characteristics of this pain phenomenon that we have named withdrawal-associated injury site pain (WISP).

2. Methods

This nonconsecutive exploratory case series was derived from data gathered through an online survey and semistructured qualitative interviews using a convergent mixed-methods design.[36,105]

We were unable to identify any previously published validated instruments to assess injury site pain during opioid withdrawal. Therefore, we created and iteratively tested a pilot survey, administering it to target populations followed by individual-focused interviews, until no further changes were required for external consistency. We developed 5 screening questions and a descriptive survey containing 35 questions, with some options for narrative responses. Survey content validity was achieved through face validation and context validation. The survey literacy level was assessed to be grade 7.4 on the Flesch–Kincaid scale.[54,79] In the survey given to participants, WISP was referred to as "recurrent pain" which was updated to WISP in Supplement 1 for congruency with this report (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A341). Instead of taking the online survey, participants living close to the research team could choose an in-person semistructured interview using online survey questions plus semistructured qualitative questions to further explore their perceptions and beliefs. The lead author (L.M. Rieb) conducted all interviews. New questions evolved as themes and nuances of the WISP experience emerged.

We enrolled a diverse cohort of patients reporting daily opioid consumption, regardless of the reason they had taken opioids (CNCP or OUD) because the neurophysiologic changes induced by opioids that affect withdrawal are likely the same in both populations.[9,62] We recruited a convenience sample using posters and bookmarks, as well as snowball sampling methods. Posters purposefully sought participants who had pain at old injury sites during opioid withdrawal and were placed at 20 facilities across Canada, including inpatient and outpatient detoxification treatment facilities, out-patient pain management clinics, primary care methadone clinics, and a local inner-city research facility, between November 2013 and June 2015. Interview participants gave written consent to participate. The University of British Columbia's Behavioral Ethics Review Board and the Vancouver Coastal Health Research Institute approved the study protocol.

Eligible participants were 18 years or older and acknowledged being able to read English at a grade 8 level or above. Individuals were excluded from the interview if they appeared impaired from substance or medication use. The 5 initial screening questions probed for the presence of WISP:

(1) Use of opioids daily for 3 months or more, and
(2) A significant painful injury that was healed and pain-free for at least 3 months before starting opioids, and
(3) During that pain-free time was off all other pain medications, and
(4) Two weeks or more off opioids since starting daily use, and
(5) Temporary return of pain at the old healed injury site when stopping opioids.

If the participant answered "yes" to all 5 screening questions, they met criteria for having WISP. These participants could choose to continue to the additional descriptive survey. Participants self-administering the online survey were given options to link to resources for emotional support, to enter a draw for a gift, and to return to the website later for a copy of the results. In addition, participants who agreed to be interviewed received a $20 honorarium. Interview recruitment continued until predominant theme saturation occurred.

Demographic characteristics of participants included in this study are summarized using descriptive statistics, reporting percentages and total counts for dichotomous or categorical values as well as medians and interquartile range (IQR) for continuous values. Quantitative frequency analysis was performed on the survey questions using SPSS V.23.

The qualitative interviews were recorded and transcribed. These qualitative data were thematically coded using NVivo version 11.1.1 (1707) by the lead author (L.M. Rieb). In analyzing these qualitative data, both deductive and inductive approaches were used,[19] beginning with themes from the survey and expanding with themes that emerged from the interviews.

3. Results

During the study period, 58 people completed screening, including 31 by interview. Among these participants, there were 47 who met criteria for WISP. The average age was 46 years (IQR: 20). Thirty-four (72%) of these participants went on to complete the full descriptive survey (23 by interview). Among those interviewed, 21 answered questions beyond the survey and are included in the qualitative analysis (2 were excluded for fatigue and confusion with open-ended questions).

The sociodemographic data of those who completed the full descriptive survey (along with the subset interviewed) are outlined in **Table 1**. For the survey, the median participant age was 45 years (IQR: 18). Most participants were male, white, unemployed, with a grade 12 education or higher. Most were recruited from an inner-city research office, followed by primary care clinics that offered methadone programs, and several from residential treatment facilities and pain clinics in British Columbia, Canada. All of the interviews took place in Vancouver. Those interviewed had similar age and sociodemographic characteristics as the overall sample.

Interspersed below with the quantitative data are participant quotes from the themes that emerged during the qualitative interviews.

3.1. Bodily experiences of withdrawal-associated injury site pain

Although there was a range of experiences reported, most participants found WISP to be intense and aversive both physically and emotionally. As one participant noted, *"Oh God, I was in hell."*

The surveyed descriptive characteristics of the experience of WISP are outlined in **Table 2**. Most participants recalled WISP as being severely painful: The most commonly recalled pain score for WISP on an 11-point Likert scale (0-10) was 8 (IQR: 2). When asked to compare intensity of pain, WISP was recalled by most participants (22; 65%) as being more painful than their generalized withdrawal pain, and as the same or less painful

Table 1

Sociodemographic characteristics.

Age of those with withdrawal-associated injury site pain (n = 47)	46; IQR 20	
Age of those who took the full survey (n = 34)	45; IQR 18	
Age of those interviewed (n = 21)	47; IQR 20	
Participant characteristics*	**Survey (n = 34), count (%)**	**Interview (n = 21), count (%)**
Sex		
Male	21 (62)	14 (66)
Female	13 (38)	7 (33)
Race/ethnicity†		
White (Caucasian)	24 (72)	13 (62)
Native (First Nations)	9 (27)	7 (33)
Black (African American)	1 (3)	1 (5)
Other	1 (3)	0 (0)
Highest education completed		
Grade 11 or less	10 (30)	6 (29)
Grade 12 or equiv.	8 (24)	4 (19)
Trade school	1 (3)	1 (5)
University, college	14 (42)	9 (41)
Missing	1 (3)	1 (5)
Current employment status		
Full-time	4 (12)	1 (5)
Part-time	7 (21)	3 (14)
Unemployed	22 (67)	16 (76)
Missing	1 (3)	1 (5)

* Of those that completed the full survey.
† Participants could choose all that applied.
IQR, interquartile range.

Table 2

WISP descriptive characteristics.

Characteristic	Count (%) (n = 34)
WISP at worst (0-10)*	
3	1 (3)
4	1 (3)
5	3 (9)
6	6 (18)
7	4 (12)
8	12 (35)
9	1 (3)
10	6 (18)
WISP versus original injury pain†	
WISP less painful than injury	16 (47)
WISP same intensity as injury	5 (15)
WISP more painful than injury	12 (35)
Cannot remember	1 (3)
WISP versus general withdrawal pain	
WISP less painful than w/d	5 (15)
WISP the same intensity as w/d‡	4 (12)
WISP more painful than w/d	22 (65)
Cannot remember	3 (9)
How long WISP versus withdrawal	
WISP lasted shorter time than w/d	15 (44)
WISP same time as w/d	6 (18)
WISP longer than w/d	13 (38)
WISP makes it harder to stop opioids	
Yes	27 (79)
No	7 (21)
WISP makes you want to use opioid	
Yes	29 (85)
No	5 (15)
Ever taken an opioid to relieve WISP	15 (44)

* If WISP occurred more than once, participant asked to recall the time WISP was most intense.
† Asked to compare the intensity of the pain.
‡ Included one who did not have withdrawal pain.
WISP, withdrawal-associated injury site pain.

than the original injury, although 13 (38%) felt WISP was even more painful than their original injury and was often compared with their original injury in quality. For example, one participant remarked on WISP being like a "*flashback of the original injury*":

> *"God, it felt just like it did when it was healing when it was broken, yeah. I don't know how—any other way to describe it." Participant #2, 53 year-old white male, original injury—fractured arm at age 12*

There was often a distinction made between WISP and generalized withdrawal pain:

> *"I was pounding my legs…old injury sites are horrendous. So, like it's more severe in those spots. The other part you can like go, get through with a hot cloth, or whatever, with Gravol and stuff, but old injury sites come back with like, severe severity." Participant #17, 58 year old Indigenous female, original injury—foot fractures requiring plating and lower leg injuries requiring fasciotomies after a home invasion, capture, and repeated assault with a hammer.*

In the interviews, some participants described potential inflammatory and neuropathic symptoms of WISP. For example:

> *"It's just almost like a shooting up the back of my leg, combined with pressure in that area, as well as, you know, I could feel my skin stretching and the sensitivity to touch was increased." Participant # 5, 35 year old white male, original injury—right ankle tendon tear requiring casting.*

The above engineer also reported swelling of his right (but not left) ankle during opioid withdrawal. In a variation on this theme, another participant endorsed always feeling stiffness along with pain at his old healed injury site:

> *"Yeah, it was restricted motion… I think the texture, the back of my wrist, I think it became a bit woody and … I deliberately went through wrist stretching exercises…[to get my] wrist flexibility back."—Participant #1, 62 year-old white male physician, original injury—soft tissue inflammation and infection in the dorsum of his left wrist from injecting fentanyl.*

This participant felt WISP and the associated stiffness were postacute withdrawal phenomena, which occurred temporarily as withdrawal faded. However, all others interviewed reported that WISP began during the time of other withdrawal features, but could extend longer. There was one participant who had no other opioid withdrawal symptom but pain at his old injury site.

Typically, participants reported that the contralateral area to the injury site did not hurt in withdrawal or did so in a manner that was "*much, much less, not even notable*." In this regard, the person acted as their own control, indicating WISP as somehow distinct from generalized withdrawal pain.

On average, participants noted it took about 2 weeks (median: 14; IQR: 24; range 1-70, with outliers at 120 and 365 days) for WISP to resolve after stopping opioids. By 30 days, WISP was finished in 28 (82%) of participants, although for 6 (18%) it lasted longer than a month.

3.2. Emotional aspects of withdrawal-associated injury site pain

Participants spoke of the "*emotional pain*" of opioid withdrawal, in general, and of WISP, in particular, during which the trauma or emotional distress associated with the original injury could be re-experienced. For example:

> *"There's also not just physical pain… I was run over by a semi so I suffered some physical injuries that come up in withdrawal, but also there's anxiety from it too…It's like PTSD from that big time"—Participant #8, 38 year old white male with previous multiple bilateral lower leg and foot fractures after being struck and pulled underneath a semi-trailer.*

3.3. Withdrawal-associated injury site pain affect on opioid use behavior

Twenty-seven survey participants (79%) felt that having WISP made it harder to come off opioids, and 29 (86%) reported that having WISP made them want to take an opioid to relieve the pain. From the interviews, it was clear that many of our participants had stopped opioids multiple times, and 15 (44%) of those surveyed reported having taken an opioid to relieve WISP during one of their attempts at detoxification. However, for a few interviewees, having WISP "*…made me glad that I stopped taking opiates.*"

3.4. Mitigators of withdrawal-associated injury site pain

There were 19/34 (56%) participants who could recall taking one or more nonopioid medications or substances that helped relieve WISP. Most of them (17 [89%]) listed non-steroidal anti-inflammatory drugs (NSAIDs), most frequent to least: ibuprofen, naproxen, and ketorolac. Six (32%) mentioned acetaminophen, and 3 (16%) listed either gabapentin or pregabalin. One person each named ketamine, phenobarbital, cyclobenzaprine, alcohol, cannabis, and a topical herbal remedy containing menthol and camphor. Several commented that opioid rotation to buprenorphine before tapering lessened WISP. One felt rotation to methadone before detoxification was helpful and another that methadone maintenance suppressed WISP; however, several participants remarked that methadone maintenance was the hardest opioid use to come off of in terms of WISP and general withdrawal symptoms. A few participants found that calming techniques assisted in lowering WISP.

Half of those surveyed believed that if they had been told by a health care provider about WISP they would have "*absolutely*" had more courage to get through the opioid cessation process.

3.5. Original injury characteristics

Characteristics of the original injury reported by participants are listed in **Table 3**. Participants reported their original injury usually as having occurred many years before the survey (median: 17; IQR: 14.5). Fracture was the most commonly reported type of injury (21 [62%] of cases) at times involving instrumentation or subsequent infection, followed by soft tissue injuries (abscesses, strain/sprains, blunt trauma, incision site pain), and one case of dislocation. Most participants rated the original injury pain as severe: On an 11-point Likert scale (0-10), the median pain was 10 (IQR: 3). The original injury pain typically lasted for weeks or months. Participants reported that they had a long pain-free span lasting months or, more commonly, years between their injury and their initiation of opioids (for a separate issue). The median time between the original injury and having WISP was 7 years (IQR: 14).

Table 3

Original injury characteristics.*

Characteristic	Count (%) (n = 34)
Type of injury	
Fracture	21 (62)
Soft tissue	12 (35)
Other	1 (3)
Original injury pain at worst (0-10)	
4	2 (6)
5	2 (6)
6	3 (9)
7	3 (9)
8	2 (12)
9	4 (12)
10	17 (52)
Original injury pain lasted	
Days	1 (3)
Weeks	13 (39)
Months	13 (39)
Years	6 (18)
How long pain-free before opioids†	
Days	1 (3)
Weeks	5 (15)
Months	10 (30)
Years	17 (52)

* Original injury site.
†Time pain-free at injury site (when off medications and street drugs) before starting opioids.

3.6. Opioid withdrawal characteristics

Characteristics of the withdrawal syndrome are listed in **Table 4**. The most commonly used opioids before cessation and experiencing WISP were morphine, heroin, oxycodone, and methadone. Most participants surveyed had stopped their opioid use abruptly. Most participants recalled significant opioid withdrawal symptoms which lasted on average 2 weeks (median: 13 days; IQR: 25; range 2-80 with an outlier at 143). By 30 days, 27 (79%) of the participants were over withdrawal. Nineteen (56%) survey participants reported restarting opioids to make generalized withdrawal symptoms go away during one of the often many attempts at detoxification.

Sixteen of those interviewed recalled the doses of the opioids used just before stopping and getting WISP. These were converted to morphine equivalent daily dose (MEDD) and averaged (**Table 5**). These high doses are conservative calculations because we did not include additional opioids used concurrently if the amount consumed was not recalled.

3.7. Theories about the origin of withdrawal-associated injury site pain

Participants tried to conceptualize WISP within the context of their lived experience. Withdrawal-associated injury site pain was characterized as a *"mystery"* by some participants. Furthermore, although there were those who expressed that it was "*all part of the drug withdrawal,"* there were others who reported that they thought they had developed a new disorder, like "*arthritis*." Still other participants believed that they had improper healing of the original injury, with one participant noting, "*I don't think it healed right."*

Table 4

Opioid withdrawal characteristics.*

Characteristic	Count (%) (n = 34)
Type of opioid used before cessation†	
Morphine	12 (35)
Heroin	12 (35)
Oxycodone	11 (32)
Methadone	10 (29)
Codeine	6 (18)
Hydromorphone	5 (15)
Meperidine	2 (6)
Opioid withdrawal symptoms†	
Low mood	33 (97)
Nausea or vomiting	26 (77)
Muscle/joint aches all over	33 (97)
Runny nose/eyes	24 (71)
Wide pupils, goose bumps, and sweat	33 (97)
Diarrhea	28 (82)
Yawning	30 (88)
Fever	21 (62)
Trouble sleeping	31 (91)
Other	15 (44)
None	0 (0)
Method of stopping opioids	
Abruptly	16 (47)
Tapering	13 (38)
Rotated opioid to taper	5 (15)
Ever taken an opioid to relieve withdrawal	19 (56)

* At the time they experienced withdrawal-associated injury site pain.
† Participants could choose all that applied.

One participant combined the view of a possible underlying injury with lack of endogenous opioids during withdrawal being the cause of WISP:

> *"I think [WISP occurs] because lack of my own body producing a pain killer. That it's just sensitive due to the injury… And when I'm in withdrawal my body's way too sensitive and there's pain there that's not being handled, right… [Then] my body kicks in its own morphine to cover up because it helps with the, I don't know, the tolerance and the damage that's done there." Participant # 8, as above.*

A number of interviewees felt that WISP "*might be psychological."* Another took this concept further and spoke of it as a "*ghost pain*." A more elaborate version of this theme was the concept of the brain trying to play a trick on the participant as part of drug craving:

Table 5

Recalled opioid dose before withdrawal-associated injury site pain WISP.

Calculation (n = 16)	MEDD* (IQR)
Oral route assumed†	
Mean	840
Median	213 (970)
Parenteral route assumed‡	
Mean	962
Median	480 (1036)

* Morphine equivalent daily dose in milligrams.
† When route not specified, and oral route assumed.
‡ When route not specified, and parenteral assumed.
IQR, interquartile range.

> *"I thought, okay, it's such a strong pull to do the drugs that my brain figured out that because I started taking opiates when I sprained my ankle, it's going to start kicking the pain out at the ankle to get more opiates…because my brain was subconsciously craving it… the primal part of my brain, it still wants to communicate. And it communicates in basic level, right. So it's going to be pain, pleasure, pain, pleasure, right… I honestly do believe it's a form of communication between the primal part of your brain and your pre-frontal cortex." Participant # 5, as above.*

Among those interviewed, a few participants experienced with multiple withdrawal episodes suggested that it was opioid use itself that not only produced WISP but after a while could cause their old healed injury sites to hurt with use:

> *"In hindsight… I never correlated oxy use to actually producing pain. And in my experience, that's pretty much what happened. Addiction promoted pain." Participant #10, 34 year-old white female, original injury—minor right knee twist playing basketball in junior high school.*

There was one participant who later had WISP, who identified that opioid use at the time of his original injury had also seemed to increase his pain:

> *"When I got beaten up, when I broke my tailbone I started using Tylenol 3s and stuff like that and then it increased it instead. That was weird." Participant #18, 39 year-old Indigenous female, original injury—coccyx fracture from being kicked.*

3.8. Current opioid use

At the time of the survey, 21 (61%) participants were no longer taking opioids, and the rest reported one or more of the following: Eleven (32%) were in a methadone or buprenorphine/naloxone maintenance program, 9 (27%) were using opioids because of addiction, 7 (21%) were using opioids for pain at a different site, and notably 6 (18%) were taking opioids for pain at the old healed injury site that they knew could be pain-free after opioid cessation.

4. Discussion

From the descriptions provided by our participants, the first clinical picture of WISP has been drawn. For those who have had a previously healed injury that was pain-free when daily opioids began, injury site pain can return with a vengeance upon opioid cessation but vanish like a wisp sometime after withdrawal is over, an experience that can influence opioid use behavior.

Participants on average rated the intensity of WISP as severe (8/10), almost as painful as their original injury (10/10), and more painful than their generalized withdrawal pain. Also some participants interviewed described neuropathic and inflammatory symptoms accompanying WISP. The severity of WISP and of the original injury pain is interesting because there is evidence that an intense barrage of pain signaling from the periphery, especially if it involves tissue inflammation, infection, or damage (as with our subjects), can alter areas of the central nervous system to become more pain sensitive, a contributor to central sensitization.[12,64,117,140–142]

Opioid use can also cause or worsen neuroimmune and neuroinflammatory responses and add to central sensitization through the release of prostaglandins, chemokines, and

cytokines (eg, tumor necrosis factor, substance P, interleukin 2), including those from microglial cells after toll-like receptor 4 stimulation.[6,39,60,68,73,80,112,133,134] Along with opioid, neurokinin 1, and toll-like receptor 4 antagonists, NSAIDS and gabapentinoids have been found to reduce neuroinflammation and mitigate OIH and/or WIH in some[1,5,14,18,34,45,46,61,70,83,85,94,100,121,127,135,137] but not all[50] circumstances. In our study, a subset of participants named NSAIDs most frequently and gabapentinoids third for relieving WISP, supporting a possible neuroinflammatory component.

Additional aspects of central sensitization that have been implicated in OIH and WIH involve changes in ascending and descending central pathways (including the dorsal horn, rostral ventromedial medulla, raphe nucleus, and somatosensory cortex) and involve gamma-Aminobutyric acid, dynorphin, cyclic adenosine monophosphate, protein kinase, glutamate, N-methyl-D-aspartate receptors, and other components.[13,15,16,22,25,26,39,43,58,86,92,93,98,128,129,145] Among our participants, just one person each named ketamine, phenobarbital, alcohol, and cannabis as relieving WISP. Although these may be coincidental, there is evidence that these or related substances may mitigate OIH, WIH, or other forms of pain through modulation of one of the above mechanisms, some of which are also involved with gabapentinoids.[6,74,94,111,113,116]

An opioid overuse pain syndrome has been previously proposed that incorporates physical and emotional components driving opioid use.[89] In the narratives reported here, physical pain and emotional suffering were intertwined during opioid withdrawal and contributed to the aversive nature of the experience of WISP. Future research may determine if WISP and potential injury site swelling may in part be caused by adrenoceptor stimulation from catecholamine release during opioid withdrawal. This mechanism has been implicated in WIH.[15] Sympathetic outflow, including anxiety states can modulate neuroinflammation and pain including joint swelling.[106,118] Norepinephrine can also induce glial cells to release proinflammatory cytokines.[60,68] Clinically, both propranolol and clonidine have been shown to decrease OIH.[28,81]

Thus, it is speculated that OIH and WIH may play key roles in WISP: As pain sensitivity increases due to opioid use, and then further during withdrawal, residual underlying sensitivity from the injury (either peripheral or central) may be uncovered, exacerbated by sympathetic outflow, including anxiety from pain.

Withdrawal-associated injury site pain was typically recalled to last about 2 weeks, similar to the timing of withdrawal. By 1 month, WISP was resolved in 82% of participants. Previous documentation has shown that the nervous system takes time to reset after prolonged opioid exposure.[95] Previous heroin users, those withdrawn from methadone, and patients with chronic low back pain withdrawn from prescription opioids have all been shown to have abnormal heat or cold pain perception for somewhere between one and 5 months after opioid cessation.[108,109,126,132] Opioid rotation before taper was reported by a few of our participants to be helpful. Unfortunately, opioid substitution therapy has not always been shown to improve OIH in heroin users and may instead worsen it,[33] although low dose methadone may assist in OIH prevention[35] and has been shown to allow pain control in cancer patients unresponsive to rapid escalation of other opioids.[96]

Our group reported extensive generalized withdrawal symptoms with opioid cessation. Two other studies in CNCP patients did not find "significant" withdrawal symptoms after opioid cessation, measuring on average 4 on the Clinical Opiate Withdrawal Scale (COWS), yet their participants had WIH to cold or heat pain.[66,144] One explanation for the discrepancy may be that a low COWS score still may be recalled as withdrawal. Other explanations may include study population differences in initial opioid dose, duration of opioid use, rate of opioid cessation, presence of opioid rotation, other medications used during tapering, and number of times detoxified—all of which have been shown to influence OIH or WIH.[14,24,30,44,47,66,74,104,124,131]

Comparatively low opioid doses, along with taper instead of abrupt cessation may in part explain why a number of studies have reported a lack of temporary CNCP pain escalation (or even improvement in pain) immediately after opioid cessation,[11,82,102,125,131] although their dropouts may have had a different experience. Also, it is unknown in the other studies if the original source of CNCP was injury.

This study further outlined participant theories regarding the etiology of WISP. Attribution of WISP to normal withdrawal, or speculation about re-injury was predicted. However, the idea that the opioid-dependent brain is sending a pain signal to try to trick the person to take more opioids was an unexpected finding. Certainly, craving is a risk factor for relapse.[138] Also evidence exists that pain modulates dopamine release from the mesolimbic system.[123] However, the concept of drug craving triggering pain has not been previously well documented. This brings up the possibility that beyond physiologic dependence, addiction may be a driver for WISP. Also, opioid-induced glial cell activation can activate systems responsible for drug reward and dependence.[31,68,69,71,101]

Some participants had insight that taking opioids may cause or contribute to WISP, and involve endogenous pain systems. Perhaps if we had not recruited specifically for those who only had injury site pain during withdrawal, we may have had more narratives demonstrating a potential link between OIH and WISP.

The vast majority of our participants felt that having WISP made it harder to come off opioids, and made them want to use an opioid again, which 44% did during one of multiple detoxification episodes. Although at the time of the survey most participants were off opioids, it is poignant that almost one-fifth of the participants had restarted opioids to relieve pain at their old healed injury site — the one they knew could be pain-free once they came off. Thus, by implication, they were taking opioids chronically to relieve WISP (although new pathology is possible). In general, for those with OUDs pain may be a risk factor for continued substance use,[40,63,107,119] yet the source of the pain is rarely differentiated,[40,78,115] so it is unknown if injury site pain was playing a role in previous study populations.

There are limitations to our study. First, it was not designed to measure prevalence. Also, pain intensity and duration may be subject to recall bias, although reliable and valid in some circumstances.[20,37,120] Technical barriers to online survey self-completion became apparent so the interview process was expanded. The principal investigator did all of the interviews and coding so there is a possibility of investigator and interview bias.[143] Information on cigarette smoking status and alcohol cessation were not elicited yet may influence the success of opioid elimination[67] and add to pain during withdrawal.[7,72] We did not question psychological status, which can affect WIH[23] and alter recalled acute pain intensity[59] and opioid utilization[48,49] as well as affect relapse and dropout rates when stopping opioids.[63,77,88] We did not look at genetic, sex, and hormonal differences, all of which can impact OIH.[75,76,87,136] Finally, we did not recruit controls with no previous significant injury, although many of our participants acted as their own control (injury-free on the contralateral side).

This research represents the first known documentation that previously healed, and pain-free injury sites can temporarily become painful again when stopping opioids. This experience

seems to be a barrier to opioid cessation and raises an important question. Are there patients labeled with CNCP who in fact have WISP? Given the findings in this study, a prospective observational cohort study could document WISP incidence, mitigating factors, influence on opioid detoxification, as well as correlation with OIH and WIH. Ultimately, a randomized controlled trial of treatments for WISP could be undertaken to reduce suffering in those individuals attempting to discontinue opioids.

Conflict of interest Statement

The authors have no conflicts of interest to declare.

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Appendix A. Supplemental Digital Content

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