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

Launette Marie Rieb,a,b,* Wendy V. Norman,a Ruth Elwood Martin,c Jonathan Berkowitzd, Evan Woodd,e Ryan McNeileb,e M.-J. Milloya,b,e

Abstract
Withdrawal pain can be a barrier to opioid cessation. Yet, little is known about 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 has spurred the need to address barriers to opioid cessation. Among these barriers, pain during or right after opioid withdrawal may be key. Generalized myalgias and arthralgias are well known to occur during opioid withdrawal, and were described as “internal rheumatism” almost 2 centuries ago. 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), which is at times confused with tolerance, which may be first described over a century ago. Opioid-induced hyperalgesia is at times confused with tolerance, which may be first described over a century ago.

Withdrawal pain can be a barrier to opioid cessation. It can be difficult for those who take opioids, and can create enormous challenges in the doctor–patient relationship. Along with the above pain syndromes, we have observed patients who report that pain can reoccur at their old, previously

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Web site (www.painjournalonline.com).

PAIN 157 (2016) 2865–2874

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http://dx.doi.org/10.1097/j.pain.0000000000000710
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. 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.

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. 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. We recruited a convenience sample using a snowball sampling method. 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, 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
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.

### Table 1  
**Sociodemographic characteristics.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survey (n = 34), count (%)</th>
<th>Interview (n = 21), count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (62)</td>
<td>14 (66)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (38)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Race/ethnicity†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (Caucasian)</td>
<td>24 (72)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Native (First Nations)</td>
<td>9 (27)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Black (African American)</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Highest education completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 11 or less</td>
<td>10 (30)</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Grade 12 or equiv.</td>
<td>8 (24)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Trade school</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>University, college</td>
<td>14 (42)</td>
<td>9 (41)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Current employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-time</td>
<td>4 (12)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Part-time</td>
<td>7 (21)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>22 (67)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (3)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

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

### Table 2  
**WISP descriptive characteristics.**

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

* † 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.
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).

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.”
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:

“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.

### Table 4

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

* At the time they experienced withdrawal-associated injury site pain.
† Participants could choose all that applied.
‡ When route not specified, and parenteral assumed.
IQR, interquartile range.

### Table 5

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

<table>
<thead>
<tr>
<th>Calculation (n = 16)</th>
<th>MEDD* (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral route assumed†</td>
<td>Mean 840</td>
</tr>
<tr>
<td></td>
<td>Median 213 (970)</td>
</tr>
<tr>
<td>Parenteral route assumed‡</td>
<td>Mean 962</td>
</tr>
<tr>
<td></td>
<td>Median 480 (1036)</td>
</tr>
</tbody>
</table>

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

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...
corticotropin-releasing factor (CRF) and possibly other neuropeptides. However, CRF immunoreactivity has changed during acute opioid withdrawal in some studies.130 In our study, a subset of participants reported increased CRF expression during opioid withdrawal.129,130 The role of CRF during opioid withdrawal is poorly understood, and more research is needed to clarify its potential involvement in the development of WISP and OIH.

In summary, we have outlined participant theories regarding the etiology of WISP and OIH. It is clear that these two conditions are complex and multifactorial, involving both pharmacologic and endogenous mechanisms. The results of this study provide a potential framework for understanding the development of WISP and OIH, and may guide future research to develop effective interventions to prevent or treat these conditions.
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.

Acknowledgements

The authors thank the study participants for their contributions to the research, as well as current and past researchers and staff. We would specifically like to thank Dr. Michael Klein for conceptual support of the original study design; Dr. Brittany Dennis for her review of the manuscript; and Dr. Kathy Hornby, Jane Liu, and Victor Trot for their research assistance. Dr. L. M. Rieb received funding through the Clinical Scholars Program, Department of Family Practice, University of British Columbia, the College of Family Physicians of BC, and the US National Institutes of Health via a National Institute of Drug Abuse (NIDA) sponsored Canadian Addiction Medicine Research Fellowship through St. Paul's Hospital (R25 DA037766-02). Dr. W. V. Norman is supported with a Chair in Applied Public Health Research from the Canadian Institutes for Health Research and the Public Health Agency of Canada, and as a Scholar of the Michael Smith Foundation for Health Research. Dr. E. Wood is supported in part by a Tier 1 Canada Research Chair in Inner-City Medicine award. Dr. M.-J. Milloy is supported in part by the United States National Institutes of Health (R01-DA051525). Drs. M.-J. Milloy and R. McNeil are supported by Scholar Awards from the Michael Smith Foundation for Health Research and New Investigator Awards from the Canadian Institutes of Health Research. The University of British Columbia has received an unstructured gift from NG Biomed to support Dr. M.-J. Milloy’s research. These funders had no role in the design and conduct of this study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article.

Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A341.

Article history:

Accepted 26 August 2016
Available online 1 September 2016

References


