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WITHDRAWAL-ASSOCIATED INJURY SITE PAIN PREVALENCE AND CORRELATES AMONG OPIOID-USING PEOPLE WHO INJECT DRUGS IN VANCOUVER, CANADA

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Abstract

Background—Pain can return temporarily to old injury sites during opioid withdrawal. The prevalence and impact of opioid withdrawal-associated injury site pain (WISP) in various groups is unknown.

Methods—Using data from observational cohorts, we estimated the prevalence and correlates of WISP among opioid-using people who inject drugs (PWID). Between June and December 2015, data on WISP and opioid use behaviours were elicited from participants in three ongoing prospective cohort studies in Vancouver, Canada, who were aged 18 years and older and who self-reported at least daily injection of heroin or non-medical prescription opioids.

Results—Among 631 individuals, 276 (43.7 %) had a healed injury (usually pain-free), among whom 112 (40.6 %) experienced WISP, representing 17.7 % of opioid-using PWID interviewed. In a multivariable logistic regression model, WISP was positively associated with having a high

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Contributors

The first author, Dr. Rieb, formulated the research question, and had the leading role in questionnaire development, conceptual and clinical interpretation, as well as manuscript writing. Corresponding author, Dr. Milloy, assisted with questionnaire development, statistical interpretation, and manuscript writing. Drs. Nosova and Hayashi assisted with statistical analysis and data interpretation, as well as manuscript writing. Co-authors Drs. Wood and DeBeck assisted with interpretation and manuscript writing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

school diploma or above (Adjusted Odds Ratio [AOR] = 2.23, 95 % Confidence Interval [CI]: 1.31–3.84), any heroin use in the last six months (AOR = 2.00, 95 % CI: 1.14–3.57), feeling daily pain that required medication (AOR = 2.06, CI: 1.18–3.63), and negatively associated with older age at first drug use (AOR = 0.96, 95 % CI: 0.93–0.99). Among 112 individuals with WISP, 79 (70.5 %) said that having this pain affected their opioid use behaviour, of whom 57 (72.2 %) used more opioids, 19 (24.1 %) avoided opioid withdrawal, while 3 (3.8 %) no longer used opioids to avoid WISP.

Conclusions—WISP is prevalent among PWID with a previous injury, and may alter opioid use patterns. Improved care strategies for WISP are warranted.

Keywords

Pain; Substance withdrawal syndrome; Opioid; Opioid dependence; Hyperalgesia; Observational cohort study

1. INTRODUCTION

According to the United Nations Office on Drugs and Crime, opioid use disorder (OUD) contributes to a growing burden of morbidity and mortality globally, especially among individuals who inject illicit opioids (UNODC, 2020). Among people with OUD, pain is a common comorbidity, has been identified as a risk factor for continued non-medical opioid use, and may impact treatment prognosis (Becker et al., 2009; Dennis et al., 2015; Edwards et al., 2011; Groenewald et al., 2019; LeBlanc et al., 2015; Rosenblum et al., 2003; Voon et al., 2018). However, few studies have delineated the components of pain that may contribute to the overall pain experience and influence opioid use behaviour among people who inject drugs (PWID). Abnormal increased pain sensitivity, also termed opioid-induced hyperalgesia, has been shown to be common in those with OUD as well as those with chronic noncancer pain on long-term opioid medication (Arout et al., 2015; Compton et al., 2012; Lee et al., 2011; Mao, 2002; Rivat and Ballantyne, 2016). Once opioid use is abruptly stopped, the underlying pronociceptive forces are further revealed and combine with the effect of catecholamine release to result in withdrawal-induced hyperalgesia that can take weeks or months to resolve (Celerier et al., 2001; Prosser et al., 2008; Treister et al., 2012).

In addition to the generalized myalgias and arthralgias, we described in a previous mixed methods study how even healed and typically pain-free injury sites can temporarily become recurrently painful during opioid withdrawal (Rieb et al., 2016). To improve diagnosis and care, we named the phenomenon withdrawal-associated injury site pain (WISP). In that study, 44 % of participants with WISP reported that this emotionally-aversive pain experience caused them to relapse to opioid use. Some participants reported neuropathic features of WISP, including shooting pain and sensitivity to touch (allodynia). We suggested a variety of possible causal mechanisms, for example, linking WISP with central sensitization, opioid-induced hyperalgesia and withdrawal-induced hyperalgesia (Hutchinson et al., 2007; Rieb et al., 2016; Rivat and Ballantyne, 2016; Woolf, 2011). We later published a case report that described these features (Rieb et al., 2018). Non-opioid medications that have previously been identified to help relieve WISP include gabapentin and non-steroidal anti-inflammatories (NSAIDs) (Rieb et al., 2018, 2016). However, the

prevalence and clinical significance of WISP in various populations have yet to be reported. To address this knowledge gap, we undertook a study of WISP among a community-recruited sample of opioid-using PWID to determine its prevalence, its self-reported impacts on opioid use behaviours, and estimate its relationship with relevant sociodemographic, structural, clinical, and behavioral factors.

2. MATERIALS AND METHODS

2.1. Cohorts and participants

The current analyses used data from three ongoing prospective cohort studies involving people who use illicit drugs in Vancouver, Canada: The Vancouver Injection Drug Users Study (VIDUS), the At-Risk Youth Study (ARYS), and the AIDS Care Cohort to evaluate Exposure to Survival Services (ACCESS). The participants in these cohorts have been recruited through self-referral, word-of-mouth, and street outreach. These cohorts, including their specific eligibility criteria, have been described in detail previously (Milloy et al., 2016; Strathdee et al., 1997; Wood, 2006). In brief, VIDUS consists of individuals aged at least 18 years who injected drugs 1 time in the 30 days prior to recruitment, and were HIV-negative at the time of enrollment. ACCESS is a cohort of HIV-positive adults who have recently used an illicit drug other than or in addition to cannabis (which was illegal during the study period) in the month prior to enrollment. Similarly, ARYS consists of street-involved youth aged between 14 and 26 years at baseline who have used illicit drugs other than or in addition to cannabis in the month prior to enrollment. In addition, all individuals must have resided in the greater Vancouver region and provided written informed consent to be eligible for the study.

2.2. Questionnaire

At baseline and semi-annually, participants completed a harmonized interviewer-administered questionnaire that elicited information on socio-demographic characteristics, drug use patterns, involvement in addiction treatment, and other relevant exposures and outcomes. Additionally, at each study visit, participants provided blood samples for HIV and HCV serologic testing and HIV disease monitoring, as appropriate. Participants were compensated for each study visit (\$30 CDN). The VIDUS, ACCESS, and ARYS studies were approved by the University of British Columbia/ Providence Health Care Research Ethics Board.

Our original mixed methods study on WISP explored in detail multiple aspects of the WISP phenomenon and allowed participants to freely express the experience in their own words. In the current study, we employed structured questions to investigate the objectives, i.e., estimate the prevalence of the WISP phenomenon and its self-reported relationship to illicit drug use patterns. For the current study, questions on the presence of WISP were added to these cohort questionnaires and administered by trained research nurses in one-on-one interviews (Fig. 1). These questions were based on findings from our previous study (Rieb et al., 2016). The questions were vetted for meaning and clarity by a focus group of the research nurses who administer the pain-related section of the questionnaire. We chose to

screen out people with only minor injuries since in our previous study most of the people reporting WISP had fractures or other significant trauma (Rieb et al., 2016).

2.3. Inclusion criteria

For the current study, we included all adult (i.e., 18 years old and older) participants interviewed between June 1 and November 30, 2015, who had, at their baseline interview, reported ever injecting drugs, and reported injecting heroin or illicit prescription opioids at least daily during the study period or in the past.

2.4. Explanatory variables

To better understand WISP, we developed a set of socio-demographic, structural, clinical, and behavioral explanatory variables we hypothesized might be correlated to the phenomenon of WISP. For example, homelessness can affect mental health and nutritional status both of which can influence pain perception. Similarly, sex differences in pain thresholds and tolerance exist so we added this variable to see if it was important for WISP. Another example of variable choice rationale is the inclusion of speedballs (co-injection of heroin and cocaine) since catecholamines can influence pain perception. The full list of variables chosen is as follows: age (continuous, per year older); sex (male vs. female); ethnicity/ancestry (white vs. nonwhite); homelessness, defined as having no fixed address, sleeping on the street, couch surfing, or staying in a shelter or hostel (yes vs. no); education (high school diploma or above vs. less than high school diploma); regular employment, defined as having a regular job, temporary work, or being self-employed (yes vs. no); and HIV status (positive vs. negative). Drug use-related variables were the following: any injection or non-injection heroin use (yes vs. no); injection speedball (i.e., a mixture of heroin and cocaine) use (yes vs. no); injection morphine use (yes vs. no); age of first illicit drug injection (continuous, per year older); and previous non-fatal overdose (yes vs. no). Other explanatory variables included: ever diagnosed with mental health illness (yes vs. no); having depressive symptoms, defined as a Centre for Epidemiologic Studies Depression (CES-D) summed score of 16 at baseline. Pain-related variables included: having any major or persistent pain (other than minor headaches, sprains, etc.) (yes vs. no); feeling some form of pain that required any pain medication (illicit or prescribed, opioid or non-opioid) each and every day (yes vs. no); ever been diagnosed with chronic pain (yes vs. no); ever been diagnosed with chronic neuropathic pain (yes vs. no); ever been diagnosed with chronic inflammatory pain (yes vs. no); ever been diagnosed with chronic muscle pain (yes vs. no); ever been diagnosed with chronic bone / mechanical / compressive pain (yes vs. no); ever been diagnosed with chronic headache / migraine (yes vs. no); taking any drugs (illicit or prescribed) for pain (yes vs. no); taking gabapentin and/or non-steroidal anti-inflammatories for pain (yes vs. no); managing pain on their own (yes vs. no); and for the sub-analysis (Table 3) of individuals, we included additional explanatory variable which measured whether individuals have requested or continued a prescription for any pain medication (yes vs. no).

All variables except for age, age of first illicit drug injection, sex, education, HIV status, and ethnicity/ancestry referred to the past six months, except if indicated otherwise.

2.5. Analysis

First, we compared characteristics of participants with an old healed injury that was typically pain free stratified by whether or not they had WISP using the Pearson's χ^2 test for binary explanatory variables and the Wilcoxon rank-sum test for continuous explanatory variables.

Second, we estimated the relationships between WISP with the socio-demographic, clinical, structural and behavioral variables defined above using bivariate and multivariate logistic regression analysis. For the multivariable models, we used an a priori-defined backward model selection procedure based on examination of Akaike Information Criterion (AIC) to fit a multivariable model (Burnham, 2002). In brief, we constructed a full model including all variables that were associated with the outcome at $p < 0.10$ in bivariable analyses. After examining the AIC of the model, we removed the variable with the largest p-value and built a reduced model. We continued this iterative process until we reached the lowest AIC score.

Third, among participants with confirmed WISP, we investigated whether or not they identified that WISP impacted the use of heroin and other opioids using descriptive statistics and logistic regression analyses.

Fourth, we assessed the association between neuropathic pain and explanatory variables among individuals who had a previous injury but did not develop WISP using logistic regression analyses.

Fifth, we looked at the correlation between pain-related variables using mean square contingency coefficient (or ϕ coefficient). We used the full sample of individuals to analyze correlation between the following variables: 1) Any major or persistent pain in the last six months; 2) Taken any drugs for your pain in the last six months; 3) Felt daily some form of pain that required medication in the last six months; 4) Have requested or continued a prescription for pain medication in the last six months; 5) Managed pain on your own in the last six months; and 6) Ever been diagnosed with a chronic pain condition. We also ran the same analysis using the sample restricted to individuals who reported ever been diagnosed with a chronic pain condition.

All p-values were two-sided. All statistical analyses were performed using R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. RESULTS

3.1. Prevalence of WISP

Between June 1, 2015 and November 30, 2015, 1298 PWID were recruited and completed a study interview, of whom 631 (48.6 %) reported at least daily injection of opioids during the study or in the past and were included in these analyses. Among the 631 PWID, 276 participants (43.7 %) reported that they had an injury that was healed and usually pain-free. Among this analytic sample of 276 PWIDs the median age was 48 years (Interquartile Range [IQR]: 37–54), 190 (68.8 %) self-identified as male, and 168 (60.9 %) reported white ethnicity. Among these individuals 112 (40.6 %) experienced the temporary return of pain to

their injury site during opioid withdrawal (thus had WISP) representing 17.7 % of all opioid-using PWID included in these analyses.

Table 1 provides baseline characteristics of the 276 PWID who have an old healed injury that is typically pain-free stratified by the presence or absence of WISP.

3.2. WISP associated factors

In a multivariable logistical regression model, WISP was positively associated with having a high school diploma or above (Adjusted Odds Ratio [AOR] = 2.23, 95 % Confidence Interval [CI]: 1.31–3.84); any heroin use (AOR = 2.00, CI: 1.14–3.57); and feeling daily pain that required medication (AOR = 2.06, CI: 1.18–3.63). Older age at first drug injection was negatively associated with having WISP (AOR = 0.96, CI: 0.93–0.99) (Table 2). Of note, having WISP was not associated with any specific type of chronic pain (including headache, muscle, bone, neuropathic or inflammatory pain) ($p > 0.05$).

3.3. WISP affect on opioid use behaviours

Among those with WISP, 79 (70.5 %) said that having this pain affected their opioid use behaviour : 57 (72.2 %) used more opioids; 19 (24.1 %) avoided opioid withdrawal; while 3 (3.8 %) no longer used opioids to avoid WISP.

3.4. Factors associated with using more opioids when WISP was present

Table 3 contains bivariate and multivariable analyses looking at the association between explanatory variables and whether pain at the old healed injury site impacted participant's use of heroin or other opioids, among 112 participants who reported WISP. In a multivariable analysis, having neuropathic pain was the only factor significantly associated with WISP and it was seemingly protective (AOR 0.25, 95 % CI: 0.08–0.72).

3.5. Factors associated with having neuropathic pain in those with a previous injury but without WISP

In Table 4, results are shown of the association between neuropathic pain and explanatory variables, among 164 PWID who had a previous injury but did not develop WISP. A statistically significant positive association was found with having neuropathic pain without WISP and taking NSAIDs and gabapentinoids (AOR = 4.06; CI: 1.13–15.09).

3.6. Correlations between pain-related variables and chronic pain

Among the full sample of 631 individuals all pairs of pain-related variables had positive moderate (ϕ : 0.30 – 0.47) to high (ϕ : 0.53 – 0.67) degree of correlation, except a single case of “Managed pain on your own” had a low correlation (ϕ = 0.17) with “requesting or continuing a prescription for pain medication”. Among the restricted sample of 368 individuals, none of the chronic pain related variables were correlated (the largest coefficient was ϕ = 0.08), except one case: Bone / mechanical / compressive pain had negative low correlation (ϕ : –0.21) with Inflammatory pain.”

4. DISCUSSION

In this study, 40.6 % of opioid using PWID reported a temporary return of pain to old healed injury sites during opioid withdrawal, thus had WISP. This represents almost one in six of all opioid-using PWID (with and without previous injury) in our sample. To our knowledge, this is the first time the prevalence of the WISP phenomenon has been estimated.

In a multivariable analysis, having WISP was not positively associated with any social, environmental, mental or physical health issue, using any other category of substance beyond opioids, nor with having chronic pain (N.B. we did not investigate changes to chronic pain in this study). Having WISP was associated with heroin use in the last six months. This observation is not surprising given that heroin is the primary drug used among illicit opioid users in Vancouver, although in recent years it has been supplanted with fentanyl (Baldwin et al., 2018). Multiple heroin withdrawal episodes, as well as high opioid doses, have been shown to increase opioid-induced hyperalgesia and withdrawal-induced hyperalgesia (Angst et al., 2003; Celerier et al., 2001, 2000; Dunbar and Pulai, 1998).

We found an association between WISP and feeling daily pain that required medication (either illicit or prescribed). Some participants may have seen their heroin use as a pain treatment, while others might have been taking prescription pain medications by mouth, insufflation or injection, possibly adding to their hyperalgesia (Celerier et al., 2000; Dunbar and Karamian, 2003; Hooten et al., 2010). Of note, methadone use (ever) was not protective against WISP in this study. Two other previous publications of former heroin users on methadone found they were abnormally sensitive on cold pressor testing (still hyperalgesic), though a different study implied mitigation of hyperalgesia at very low methadone doses in palliative patients (the low opioid dose and use of halperodol may have confounded their results for applicability to our sample) (Compton et al., 2001; Craig, 2013; Doherty et al., 2001).

In our current study, older age at first drug injection was negatively associated with WISP, indicating individuals younger at the time of their first non-medical drug injection had a higher risk of having WISP. This added sensitivity might be due to adaptations in the nervous system when exposed to opioids during adolescence or early adulthood, or from length of exposure to the opioid contributing to pain sensitivity. Studies have found chronic pain in adolescence, as well adolescent non-medical use of opioids have both been associated with OUD in adulthood (Groenewald et al., 2019; McCabe et al., 2016).

The majority of participants in this study identified that having WISP impacted their opioid use behavior, primarily by causing them to take more opioids to avoid withdrawal. We found in our previous mixed methods study that participants often described WISP not only as severely painful, but also as emotionally aversive and stressful, in keeping with the concept that substance use, pain and/or trauma can activate both pain and anxiety sensitization, heightening the chance of reinitiation of drug use (Egli et al., 2012; Uhl et al., 2019). This finding is in alignment with other research indicating that withdrawal even from non-opioid substances like alcohol and nicotine can also increase pain sensitivity (Apkarian et al., 2013; Baiaamonte et al., 2014; Egli et al., 2012).

In the multivariable subanalysis, neuropathic pain was negatively associated with taking more opioids to avoid WISP, initially implying that it was protective. People who inject drugs are at increased risk of contracting blood borne viruses like the human immunodeficiency virus (HIV), and thus to have HIV neuropathy and take medications to treat it. Nerve injury can predispose one to the formation of tolerance and opioid-induced hyperalgesia, while opioid use can perpetuate neuropathic pain (Hutchinson et al., 2008). If WISP is a clinical correlate of opioid-induced hyperalgesia then those with HIV neuropathy abruptly stopping opioids may be predisposed to experience WISP. Therefore, a subanalysis was done among PWID with a previous injury but without WISP which revealed that having neuropathic pain was associated with being on NSAIDs and gabapentin (Table 4). This finding points to the possibility that these medications may be the reason (confounder) that having neuropathic pain appeared protective against taking more opioids in the presence of WISP.

Gabapentinoids and NSAIDs, among other medications, have been shown in clinical and pre-clinical trials to reduce opioid-induced hyperalgesia and withdrawal-induced hyperalgesia through a variety of mechanisms, and were named as mitigators of WISP by participants in our previous research (Arout et al., 2015; Compton et al., 2010; Dunbar et al., 2007; Kang et al., 2002; Lee et al., 2013; Ramasubbu and Gupta, 2011; Rieb et al., 2018, 2016). Catecholamine release can cause neuroimmune changes leading to neuroinflammation, and has been implicated as one of the mechanisms of opioid withdrawal hyperalgesia (Arout et al., 2015; Drummond, 2001; Martelli et al., 2014; Pongratz and Straub, 2014; Raghavendra et al., 2002). It is thus theoretically possible that there is a neuroinflammatory component to WISP that NSAIDs and gabapentinoids may reduce in those with neuropathy. Mitigating the pronociceptive changes induced by opioid use and withdrawal can enhance treatment options for both pain and OUDs (Arout et al., 2015; Puig and Gutstein, 2017; Volkow and McLellan, 2016). There may not have been enough people taking these medications to report a clinically significant difference in experiencing WISP or altering opioid use behaviour in the presence of WISP in our overall sample of PWIDs with an old healed injury that is typically pain-free (Table 2, Table 3).

Our study adds to evidence to support the view that substance use disorders and pain may be bidirectional risk factors, i.e., one can increase the likelihood of the other through dysregulation of the nervous system (Becker et al., 2009; Edwards et al., 2011; Egli et al., 2012; LeBlanc et al., 2015; Rivat and Ballantyne, 2016; Voon et al., 2018; Watkins et al., 2009). Also the brain in pain comes to look like the addicted brain and vice versa through reorganization of the mesocorticolimbic circuitry including dysregulation of the nucleus accumbens, amygdala and prefrontal cortex, while the latter can show loss of gray matter in both conditions (Apkarian, 2011; Apkarian et al., 2013, 2004; Barroso et al., 2020; Borsook et al., 2016, 2018; Elman and Borsook, 2016). There are other lines of research showing how both pain and pain relief can be reinforcing through activation of reward circuitry (Borsook et al., 2016; Elman and Borsook, 2016; Hutchinson et al., 2012; Navratilova et al., 2012). This may help to explain why the opioid use behavior is repeated despite such emotionally aversive pain experiences, including WISP: the opioid, the pain, and the pain relief may each contribute to the addiction.

There are a number of potential limitations to our study. The first limitation has to do with generalizability. The people surveyed were primarily white and Indigenous PWID in their mid-40 s. We do not know if other population groups, age groups, non-injection opioid users, and those who use opioids for chronic noncancer pain alone will have the same prevalence of WISP, in particular those with refractory dependence on opioid analgesics (Ballantyne et al., 2019). These data may not be generalizable to PWID in other settings since our cohorts are not random samples of PWID. There is the potential for recall error and socially-desirable responding in self-reported data. However, previous studies have supported the validity and reliability of self-reported drug use data (Darke, 1998).

In the current study we are unable to know if WISP was more prevalent in those with more recently experienced injuries. Another limitation is that we could not ask about buprenorphine-naloxone use in this population. This medication came on the market in Canada late compared to availability in the US and the three cohort studies we added our questions to did not ask about it during the study period. Thus left unanswered is whether or not buprenorphine would be a mitigator of WISP in the current study population as indicated by some but not all other studies on pain in opioid users (Compton et al., 2012; Daitch et al., 2014, 2012; Ravn et al., 2013; Rieb et al., 2018).

An additional limitation to the study is that we did not ask details about their injury sites that always hurt (i.e., their sites of chronic pain), how much more these sites might hurt during opioid withdrawal, and if any added pain fades once withdrawal is over. Thus, the prevalence of WISP in our current study may just be one component of pain induced by opioid withdrawal. Another potential source of underestimation of WISP is that we included only people with “a serious physical injury”, thus potentially leaving out people with minor injuries or incisional pain that may also have experienced WISP.

Future studies could test the relationship between WISP and opioid-induced hyperalgesia, neuropathic pain and focus on potential treatments.

5. CONCLUSION

We found that over 40 % of a community-recruited sample of opioid-using PWID with previous injuries had pain return temporarily to those injury sites upon opioid cessation. Withdrawal-associated injury site pain was identified as contributing to ongoing opioid use in the vast majority of those with this type of pain experience. Thus WISP may be one of the hidden drivers of continued opioid use in PWID. Further research is needed to better understand WISP and inform future clinical trials on pharmacological and non-pharmacological treatments to mitigate pain experienced during withdrawal from opioids.

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HIGHLIGHTS

- Pain can return to previously pain-free injury sites during opioid withdrawal
- This pain is highly prevalent among opioid using people who inject drugs
- Having this type of pain perpetuates opioid use behavior
- Withdrawal-associated injury site pain is clinically relevant

1. Have you ever had a serious physical injury like a broken limb or other physical trauma that healed and is usually pain free?	Yes	No (stop)
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(If yes) nurse shows chart of prescription opioid drug names and pictures

2. During withdrawal from heroin or other opioids, have you ever experienced the temporary return of pain focused at one of your old healed injury sites?	Yes	No (stop)
3. Does this pain at your old healed injury site impact your use of heroin or other opioids?	Yes	No (Stop)
4. How?		
a) I use more opioids to relieve this pain when it occurs	Yes	No
b) I avoid opioid withdrawal to avoid this pain (i.e. continue to use)	Yes	No
c) I no longer use opioids to avoid the return of this pain during opioid withdrawal	Yes	No
d) Other _____		

Figure 1.

WISP-specific screening questions

Table 1.

Baseline characteristics^a of participants with a healed injury that was typically pain free stratified by the occurrence of WISP (n=276).

	Presence of WISP		<i>p</i> Value
	Yes (%) (<i>n</i> = 112)	No (%) (<i>n</i> = 164)	
Age (Median, IQR ^d)	46 (36–53)	48 (38–55)	0.166
Male sex (n, %)	77 (68.8)	113 (68.9)	0.979
White ancestry (n, %)	69 (61.6)	99 (60.4)	0.836
Homelessness ^c (n, %)	108 (96.4)	157 (95.7)	0.771
High school diploma (n, %)	65 (58.0)	67 (40.9)	0.006
Employment ^b (n, %)	30 (26.8)	48 (29.3)	0.653
Any heroin used ^b (n, %)	80 (71.4)	99 (60.4)	0.059
Any speedball injection ^b (n, %)	10 (8.9)	12 (7.3)	0.627
Any morphine injection ^b (n, %)	25 (22.3)	23 (14.0)	0.074
Non-fatal overdose ^c (n, %)	83 (74.1)	123 (75.0)	0.867
Age at first injection (Median, IQR ^d)	17 (15–22)	19 (16–25)	0.004
CES-D ^e score 16 (n, %)	68 (60.7)	104 (63.4)	0.760
HIV seropositivity ^b (n, %)	30 (26.8)	46 (28.1)	0.853
Diagnosed with a mental illness ^c (n, %)	79 (70.5)	101 (61.6)	0.101
Been on methadone treatment ^c	102 (91.1)	143 (87.2)	0.317
Major pain ^b (n, %)	80 (71.4)	97 (59.2)	0.037
Taken any drugs for your pain ^b (n, %)	79 (70.5)	88 (53.7)	0.005
Felt daily pain that required medication ^b (n, %)	70 (62.5)	61 (37.2)	<0.001
Taking gabapentin and/or non-steroidal anti-inflammatories ^b (n, %)	10 (8.9)	12 (7.3)	0.627
Managed pain on their own ^b (n, %)	86 (76.8)	110 (67.1)	0.081
Diagnosed with chronic pain ^c	81 (72.3)	91 (55.5)	0.005
Diagnosed with a chronic neuropathic pain ^c	26 (23.2)	23 (14.0)	0.322
Diagnosed with a chronic inflammatory pain ^c	51 (45.5)	50 (30.5)	0.286
Diagnosed with a chronic muscle pain ^c	12 (10.7)	15 (9.2)	0.764
Diagnosed with a chronic bone / mechanical / compressive pain ^c	56 (50.0)	59 (36.0)	0.550
Diagnosed with a chronic headache / migraine ^c	7 (6.3)	4 (2.4)	0.256
Have requested or continued a prescription for pain medication ^b	42 (37.5)	58 (35.37)	0.717

^aCharacteristics reported at time of study enrollment

^bDuring the last six months

^c Ever experienced

^d Inter-quartile range

^e Center for Epidemiological Studies—Depression

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Table 2.

Bivariable and multivariable logistic regression analysis of factors associated with having WISP among participants with a previously healed injury that is typically pain free (n=276).

Characteristic	Unadjusted		Adjusted	
	Odds ratio (95 % CI)	p value	Odds ratio (95 % CI)	p value
Age, per year	0.99 (0.97–1.01)	0.216		
Male sex	0.99 (0.59–1.68)	0.979		
White ancestry	1.05 (0.64–1.73)	0.836		
Homelessness ^b	1.20 (0.36–4.69)	0.772		
High school diploma	1.98 (1.22–3.25)	0.006	2.23 (1.31–3.84)	0.003
Any employment ^a	0.88 (0.51–1.51)	0.653		
Any heroin used ^a	1.64 (0.99–2.77)	0.060	2.00 (1.14–3.57)	0.017
Injection speedball (heroin and cocaine) use ^a	1.24 (0.51–2.99)	0.628		
Injection morphine use ^a	1.76 (0.94–3.31)	0.076		
Non-fatal overdose ^b	0.95 (0.55–1.67)	0.867		
Age when first illicit drug injected, per 10 years older	0.64 (0.44–0.90)	0.014	0.96 (0.93–0.99)	0.023
Depression score equal or over 16 on CES-D	1.10 (0.60–2.05)	0.760		
HIV seropositivity ^a	0.95 (0.55–1.63)	0.853		
Been diagnosed with a mental illness ^b	1.54 (0.92–2.60)	0.102		
Been on methadone treatment ^b	1.50 (0.69–3.45)	0.319		
Major pain ^a	1.73 (1.04–2.91)	0.038		
Taken any drugs for your pain ^a	2.07 (1.25–3.47)	0.005		
Felt daily pain that required medication ^a	2.81 (1.72–4.65)	<0.001	2.06 (1.18–3.63)	0.012
Taking gabapentin and/or non-steroidal anti-inflammatories ^a	1.24 (0.51–2.99)	0.628		
Managed pain on your own ^a	1.62 (0.95–2.83)	0.082		
Diagnosed with chronic pain ^b	2.10 (1.26–3.54)	0.005	1.68 (0.93–3.06)	0.087
Diagnosed with a chronic neuropathic pain ^b	1.40 (0.72–2.73)	0.323		
Diagnosed with a chronic inflammatory pain ^b	1.39 (0.76–2.58)	0.287		
Diagnosed with a chronic muscle pain ^b	0.88 (0.38–2.01)	0.764		
Diagnosed with a chronic bone / mechanical / compressive pain ^b	1.22 (0.64–2.31)	0.550		
Diagnosed with a chronic headache / migraine ^b	2.06 (0.60–8.11)	0.264		

^aDuring the last six months

^bEver experienced

Table 3.

Bivariable and multivariable Logistic regression analysis of factors associated with pain impacting the use of heroin and other opioids among people who experienced the temporary return of pain to their injury site during opioid withdrawal (n = 112).

Characteristic	Unadjusted		Adjusted	
	Odds ratio (95 % CI)	p value	Odds ratio (95 % CI)	p value
Age, per year	0.99 (0.95–1.02)	0.545		
Sex, male	1.68 (0.71–3.95)	0.232		
White race	0.73 (0.31–1.70)	0.477		
Homelessness ^b	0.79 (0.04–6.45)	0.842		
High school completion or higher	0.74 (0.31–1.69)	0.481		
Any employment ^a	0.97 (0.39–2.49)	0.940		
Any heroin used ^a	2.50 (1.05–5.99)	0.039		
Injection speedball (heroin and cocaine) use ^a	4.11 (0.73–77.48)	0.188		
Injection morphine use ^a	1.43 (0.53–4.27)	0.498		
Non-fatal overdose ^b	0.70 (0.25–1.78)	0.466		
Age when first illicit drug injected, per 10 years older	1.04 (0.60–1.89)	0.903		
Depression score equal or over 16 on CES-D	1.30 (0.44–3.62)	0.627		
HIV seropositivity ^a	2.00 (0.77–5.92)	0.177		
Been diagnosed with a mental illness ^b	0.72 (0.27–1.78)	0.489		
Been on methadone treatment ^b	1.03 (0.21–3.98)	0.969		
Taking gabapentin and/or non-steroidal anti-inflammatories ^a	0.97 (0.25–4.74)	0.969		
Have requested or continued a prescription for pain medication ^a	2.96 (1.20–8.11)	0.025	2.91 (1.02–9.26)	0.055
Managed pain on your own ^a	1.08 (0.40–2.76)	0.868		
Diagnosed with a chronic neuropathic pain ^b	0.29 (0.10–0.80)	0.017	0.25 (0.08–0.72)	0.012
Diagnosed with a chronic inflammatory pain ^b	0.50 (0.16–1.40)	0.203		
Diagnosed with a chronic muscle pain ^b	1.22 (0.33–5.94)	0.778		
Diagnosed with a chronic bone / mechanical / compressive pain ^b	2.21 (0.79–6.11)	0.126		
Diagnosed with a chronic headache / migraine ^b	2.54 (0.40–49.43)	0.401		

^aDuring the last six months

^bEver experienced

Table 4.

Bivariable and multivariable logistic regression analysis of factors associated with having neuropathic pain among participants with a previous injury who did not develop WISP (n = 164).

Characteristic	Unadjusted		Adjusted	
	Odds ratio (95 % CI)	p value	Odds ratio (95 % CI)	p value
Taking gabapentin and/or non-steroidal anti-inflammatories ^a	3.81 (1.15–12.75)	0.027	4.06 (1.13–15.09)	0.032
Age, per year	1.05 (1.00–1.11)	0.086		
Sex, male	0.65 (0.24–1.78)	0.389		
White race	2.68 (0.94–8.86)	0.080	2.29 (0.76–7.88)	0.157
Homelessness ^b	0.20 (0.03–1.30)	0.092	0.23 (0.03–1.67)	0.148
High school completion or higher	1.41 (0.54–3.69)	0.481		
Any employment ^a	0.54 (0.16–1.56)	0.282		
Any heroin used ^a	0.63 (0.24–1.66)	0.350		
Injection speedball (heroin and cocaine) use ^a	3.14 (0.36–27.53)	0.267		
Injection morphine use ^a	1.83 (0.56–5.58)	0.296		
Non-fatal overdose ^b	0.76 (0.27–2.26)	0.610		
Age when first illicit drug injected, per 10 years older	0.94 (0.48–1.73)	0.837		
Depression score equal or over 16 on CES-D	1.62 (0.50–6.27)	0.443		
HIV seropositivity ^a	2.55 (0.95–6.86)	0.061	2.72 (0.94–8.02)	0.064
Been diagnosed with a mental illness ^b	2.52 (0.89–8.35)	0.100		
Been on methadone treatment ^b	0.48 (0.14–1.75)	0.244		
Managed pain on your own ^a	0.85 (0.28–2.94)	0.785		
Diagnosed with a chronic inflammatory pain ^b	1.38 (0.53–3.73)	0.510		
Diagnosed with a chronic muscle pain ^b	0.40 (0.06–1.63)	0.257		
Diagnosed with a chronic bone / mechanical / compressive pain ^b	1.02 (0.39–2.86)	0.965		

^aDuring the last six months

^bEver experienced