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Understanding the health and service needs of diverse populations of pharmaceutical opioid users: Cohort studies of dependent users in treatment, and people who inject drugs.

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ABSTRACT

Background: This technical report summarises and compares the data collected across two time periods from two groups who use pharmaceutical opioids, those seeking treatment for PO dependence and those that inject drugs regularly.

Methods: Six local health districts were utilised to recruit the treatment cohort (n=108). The cohort of people who inject drugs (PWID) were recruited through established studies at the National Drug and Alcohol Research Centre (NDARC) and snowballing (n=133). For the treatment cohort, baseline interviews were conducted between July 2013 and April 2014 and 94% completed a three month follow up interview (n=102). For the PWID cohort, rolling cohort entry occurred between July 2013 and June 2014, and the follow up interview rate was 76%. Data were collected on a range of physical and mental health domains, substance use and treatment experience.

Results: Both cohorts reported high levels of mental and physical health co-morbidity, with a general pattern of more severe physical and mental health problems among the treatment cohort. Substance use was generally stable over the two interviews in both cohorts, with those newer in treatment reporting greater reduction in opioid use in the POUT cohort, and a reduction in oxycodone injection in the PWID cohort.

Conclusions*:* These studies represent the first Australian studies to examine pharmaceutical opioid use in detail in diverse clinical populations. Findings highlight complexities in treatment presentations with multiple co-morbid health conditions and significant numbers reporting current chronic pain amongst both cohorts. Ongoing monitoring of harms in these cohorts is essential - both cohorts displayed complex clinical profiles. Despite low levels of illicit drug use and injection among the treatrment cohort participants, this cohort typically displayed more severe clinical profiles. Despite this, the treatment cohort reported high levels of retention and low levels of substance use at the follow-up interview, and reported generally positive treatment experiences. Mental health interventions for both these cohorts are warranted.

1.0 INTRODUCTION

Incidence of pharmaceutical opioid-related problems appears to be markedly increasing in Australia. From 1992-2007, the number of opioid prescriptions in Australia increased by around 300% [1]. This increase in prescribing has been accompanied by an increase problematic use and opioid-related harms including hospital presentations[2] and mortality, with the majority of opioid deaths in Australia now involving opioid other than heroin [3].

Problematic pharmaceutical opioid use is associated with significant public health burden, yet the full extent harms and outcomes amongst different populations of pharmaceutical opioid users has not been quantified in Australia. The identified harms include dependence, overdose, injection-related injuries and diseases, and mortality [4-6]. Treatment needs for these groups are not well understood; demographic characteristics appear different from traditional drug treatment samples [7]. There is a limited evidence base as to the effectiveness of current treatments specifically for PO dependence, as research for most treatments was conducted with primarily heroin users. Further, illicit PO use may reflect unmet treatment needs. Pharmaceutical opioid users with acute and/or chronic pain present specific clinical challenges with regards to medication selection, monitoring of aberrant behaviours (e.g. poor medication control, dose escalation, diversion) and responses to non-adherence.

1.1 Study aims

To provide the first detailed studies of two diverse groups of pharmaceutical opioid users: people seeking treatment for pharmaceutical opioid dependence, and people who inject drugs (PWID), including a three month follow up to understand outcomes and interventions that are relevant to these distinct populations of pharmaceutical opioid users.

2.0 METHOD

2.1 Participant recruitment

2.1.1 Pharmaceutical opioid users seeking treatment (POUT Cohort)

Participants in the treatment cohort were recruited from community and specialist drug treatment services in six local health districts in New South Wales: Sydney Local Health District (LHD), South Eastern Sydney LHD, Northern Sydney LHD, Hunter New England LHD, Northern NSW LHD and Western Sydney LHD.

Eligibility criteria for the POUT cohort were that participants:

1. Had entered any form of drug treatment where a pharmaceutical opioid was the primary drug of concern
2. Were able to understand English sufficiently to give informed consent and participate in the study (including providing locator information for follow-up)

There was no age restriction, though participants were only recruited through adult drug and alcohol services.

2.1.2 People who inject drugs (PWID)

Participants in the prospective PWID cohort were recruited through existing studies at the National Drug and Alcohol Research Centre (Illicit Drug Reporting System, or IDRS), researcher contacts and snowballing. There was rolling cohort entry, with participants interviewed at two time-points (3-6 months apart). Baseline interviews were conducted June 2013-June 2014.

Eligibility criteria for the PWID cohort were that participants

1. Were aged >18 years of age
2. Reported injecting on a monthly or more frequent basis in the past six months
3. Residing in Sydney for the past six months

2.2 Measures

Key measures included: demographic characteristics, opioid history and current use, current pain (as measured by the Brief Pain Inventory, BPI) [8, 9], pain self-efficacy (using the Pain Self-Efficacy Questionnaire)[10], health service utilisation, alcohol and illicit drug history and current use, aberrant behaviours associated with drug use (ORBIT) [11], sleep

patterns (using the Medical Outcomes Study (MOS) sleep scale) and social support (SC). Also mental health evaluations assessing generalised anxiety disorder (GAD-7) [12], depression (PHQ-9) [12] and post traumatic distress disorder (PC-PTSD) [13].

Moderate to severe depression were defined as a score of ≥ 10 on the PHQ-9 [14], moderate to severe anxiety was defined as a score of ≥ on the GAD-7 [15], and a score of ≥ 3 on the PC-PTSD indicated a consideration for PTSD diagnosis [13].

Percentages, 95% confidence intervals (CIs) and Chi-square tests of significance are used to examine differences in proportions for independent samples. For continuous, normally distributed variables, independent samples t-tests are used to examine differences. For continuous variables with skewed distribution, medians and Mann-Whitney's U-test for significant differences are reported.

To compare changes from baseline to three months paired t-tests were used for continuous variables, and McNemars test for related variables was used for dichotomous variables. Where less than 5 were reported in 80% or more cells Fischer's exact test was used.

All analyses were conducted in SPSS Version 22.0.

2.3 Ethics approval

The current research was conducted in conformity with the *National Statement on Ethical Conduct in Human Research (2007).* Ethical approval for the POUT cohort was sought from Royal Prince Alfred Hospital Human Research Ethics Committee (HREC), and HRECs for the six relevant LHDs; Sydney LHD, South Eastern Sydney LHD, Northern Sydney LHD, Hunter New England LHD, Northern NSW LHD and Western Sydney LHD. Ethical approval for the PWID cohort was sought from UNSW HREC and New South Wales Health HRECs for Sydney LHD (lead HREC), South Eastern Sydney LHD and South Western LHD.

3.0 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE COHORTS AT BASELINE

3.1 Demographic characteristics

(i) POUT cohort

A total of 176 potential participants were referred to the POUT study, of which 108 were contactable, eligible and able to complete the interview (See Appendix 1). The POUT cohort was just over half female, mostly born in Australia with a mean age of 40.7 (S.D 10.5) years. Most were not currently employed (See Table 1).

(ii) PWID cohort

A total of 188 potential participants were referred to the PWID cohort study, of which 133 were contactable, eligible and able to complete the interview (See Appendix 1). Compared with the POUT cohort, larger proportions of the PWID cohort were male. The PWID cohort reported a mean age of 40.2 (SD 9.5) years. Both cohorts displayed high levels of social disadvantage, but compared to the POUT cohort, PWID were more likely to report completing 10 or less years of school education, a prison history (68%), living alone and unemployment (Table 1).

Table 1 : Demographic characteristics of the POUT and PWID cohorts at baseline

	POUT (n=108)	**PWID** (n=133)
Mean age (SD)	40.66 (10.53)	40.22 (9.56)
Male (%)	48.1	60.2
Born in Australia (%)	81.5	NA
Prison history	NA	68.1
Aboriginal and/or Torres Strait Islander (%)	11.1	NA
Education Level Completed (%)		
Completed Year 10 or less (%)	47.2	76.2^
Completed Year 12 or TAFE/Technical College	33.3	20.0^
Completed Tertiary qualifications	19.4	NA
Relationship Status (%)		
Never married	43.5	17.8^
Married/Defacto	34.3	16.7^
Separated/Divorced/Widowed	22.2	12.5^
Employment status (%)		
Employed/Student	29.0	3.0
Unemployed	68.2	97.0
Other (including homemaker/retired)	2.8	NA
Weekly income (%)		
$800 or more	12.5	0
$400 – 799	35.5	8.3
$399 or less	52.0	91.7
Housing (%)		
Own	15.7	16.7^
Rent (private)	48.1	75.0^
Rent (public housing)	20.4	NA
Other (incl. boarding and caravan park)	15.7	9.3^
Homeless	0.0	0.0
Living with (%)		
Alone	32.4	58.3^
Partner +/- children	30.5	4.2
Living with children alone	10.2	NA
Other	26.9	37.5^

Notes: NA= Not Asked; † = past 6 months; ^Only a small subsample were asked this question (n=25).

3.2 Physical health

3.2.1 POUT cohort

The POUT cohort reported significant morbidity with most (85%) reporting a problematic pain condition in the past 12 months (Table 2). The most common pain condition reported was chronic back or neck problems, reported by 52% as being currently problematic. Not all of these participants reported pain on the day of the interview, with 41% reporting current pain, and 38% reporting experiencing chronic pain at the time of the baseline interview. For those with current pain, the mean Brief Pain Inventory (BPI) scores reflected moderate pain interference (scores of 5-6 are considered 'moderate') and mild pain severity (scores 1-4 are considered 'mild') (Table 2). A range of other physical health problems were reported by POUT participants, the most common being sleep apnea (15.7%) and high blood pressure (11.1%).

3.2.2 PWID cohort

Although fewer PWID cohort participants reported current pain than POUT participants, a substantial minority (30%) reported currently experiencing pain other than everyday types of pain. PWID also reported a range of chronic pain conditions (Table 1 below), with 37% reporting chronic back or neck problems being currently problematic. Among those who reported current pain, the BPI severity and interference scores were lower than those reported by POUT participants (Table 2). In general, however, fewer PWID reported chronic physical health conditions compared to POUT participants.

Table 2: Physical health of the POUT vs. PWID cohorts at baseline

	POUT (n = 108)	PWID (n=133)
Currently experiencing pain (%)	40.7	30.1
Currently experiencing chronic pain (%)	38.0	NA
Problematic pain in past 12 months† (%)	85.2	49.6
Mean BPI interference score (SD)*	6.01 (2.25)	4.49 (2.91)
Mean BPI severity score (SD)*	4.42 (1.79)	3.92 (2.07)
Chronic pain conditions problematic in past 12 months		
Arthritis/Rheumatism (%)	26.9	18.2
Chronic back/neck problems (%)	51.9	37.3
Frequent/severe headaches (%)	25.0	22.9
Visceral pain (%)	21.3	18.3
Generalised pain (%)	25.0	16.5
Other physical health conditions problematic in past 12 months		
Stroke (%)	3.7	-
Heart attack (%)	0.9	0.9
Sleep apnea (%)	15.7	25.7
High Blood Pressure (%)	11.1	-
Chronic lung disease (%)	5.6	7.3
Diabetes (%)	7.4	2.8
Epilepsy (%)	1.9	2.8
Cancer (%)	1.9	0.9
Any other chronic condition (%)	24.1	11.9
Mean hours of sleep per night (SD)	6.99 (2.42)	6.8 (2.6)
Mean Sleep Problem Index II score (SD)	42.47 (23.77)	41.8 (22.7)
Mean SF-12 Physical Component Score (SD)	40.35 (10.59)	NA

Note: * = excludes cases not experiencing pain. BPI= Brief Pain Inventory, †Problematic pain condition may include chronic back or neck problems, Frequent or severe headaches, arthritis or rheumatism, visceral pain or generalised pain (eg fibromyalgia), or other chronic pain condition that was problematic in the past 12 months.

3.3 Mental health

3.3.1 POUT cohort

The POUT cohort reported complex mental health co-morbidity, with 70% reporting at least one co-morbid mental health condition in the past 12 months (excluding substance use disorder) (Table 3). Depression and anxiety/panic disorder were reported by 61% and 54% of the sample respectively. Eighty two percent of the sample reported lifetime trauma, 48% reported childhood physical abuse, 40% reported childhood sexual abuse and 62% reported childhood emotional abuse, one in three (32%) screened positive for PTSD . More than half (55%) of the sample self-reported at least two mental health conditions that were problematic in the past 12 months (excluding substance use disorders). Almost a third (29%) reported three or more co-morbid mental health conditions that were problematic in the past 12 months (range 0–6).

3.3.2 PWID cohort

The PWID cohort also reported complex mental health co-morbidity (Table 3), with 84% reporting at least one comorbid mental health condition in the past 12 months (excluding substance use disorder). On average, PWID participants reported a median of two mental health problems in the past year. Forty-five percent of the PWID sample met criteria for current moderate-severe depression, and one in four (26%) PWID met criteria for moderate-severe anxiety. Eighty-two percent of PWID had experienced a lifetime trauma, and 41% screened positive for current PTSD. Childhood physical, sexual or emotional abuse was common, with 78% reporting at least one form of childhood maltreatment. Almost half the sample (45%) reported lifetime suicidal ideation.

Table 3: Mental health, social support and quality of life of the POUT and PWID cohorts at baseline

	POUT (N= 108)		PWID (N=133)	
Self-reported diagnoses (%)	**Lifetime**	**Problematic in past 12 months**	**Lifetime diagnosis**	**Problematic in past 12 months**
Depression	81.5	61.1	67.9	48.2
Anxiety/panic disorder	66.7	53.7	60.7	46.4
Bipolar	16.7	12.0	18.0	10.1
OCD	17.6	13.9	16.1	10.1
Schizophrenia	8.3	5.6	16.2	10.1
Psychosis	8.3	5.6	21.6	9.1
Substance abuse	90.7	72.2	85.7	72.1
ADD/ADHD	7.4	2.8	13.5	7.3
Personality disorder	9.3	7.4	9.0	6.4
Median number of mental health problems in the past 12 months (Range) (above sum)	2 (0-7)		2 (0-8)	
Meeting criteria (%)				
Mod-severe depression (PHQ-9)	51.8		45.3	
Mod-Severe anxiety (GAD-7)	38.9		26.4	
PTSD	32.4		42.0	
Suicidality (%)				
Ever thought of suicide	59.3		45.0	
Mean age first thoughts (SD)	25.0(13.0)		25.2 (10.8)	
Ever planned suicide	31.5		29.3	
Ever attempted suicide	30.6		23.5	
Mean age first attempted (SD)	32 (20.1)		24.6 (9.9)	
Attempted suicide past 12 mths	5.6		3.8	
Experienced lifetime trauma (%)	81.5		81.8	
Childhood maltreatment (%)				
Physical	48.1		45.1	
Sexual	39.8		45.1	
Emotional	63.9		67.3	
Mean (SD) of the Mental Health Component Score (SF-12)	38.43 (12.1)		NA	
Mean Social Support score (SD)	3.29 (1.1)		3.34 (1.1)	
Quality of Life				
Dissatisfaction with life (%)	25.0		19.1	
Dissatisfaction with health (%)	38.0		29.7	

3.4 Drug treatment and other health service utilisation

3.4.1 POUT cohort

Most participants in the POUT cohort had previously experienced some form of drug or alcohol treatment, with a third (32%) entering treatment for the first time in their current treatment (Table 4). Opioid substitution treatment was the most common current and previous treatment, with over half (55%) currently receiving buprenorphine maintenance treatment. The median treatment length at baseline was just under one year.

Table 4: Drug treatment history among POUT participants at baseline

	POUT (n = 108)
Current TM is first episode (%)	32.0
Previous drug treatments (%)	
Managed with prescribed opioids†	11.1
Methadone	24.1
Buprenorphine+/-Naloxone	27.8
Inpatient Detoxification	30.6
Counselling	17.6
Home detoxification	10.2
Residential Rehabilitation	3.7
Naltrexone (+/- rapid detox)	1.9
Currently in OST Treatment (%)	96.3
Methadone	37.0
Buprenorphine (+/- naloxone)	54.6
Counselling	37.0
Managed with prescribed opioids (other than OST)	1.9
Duration in months of current treatment, median (Inter Quartile Range)	11.88 (22.08)
Treatments ever accessed** (%)	
AA/NA	6.5
Psychologist	72.6
Psychiatrist	74.5
Counsellor/Social worker	71.7

Note: * = in the last month. ** = ever had access. OST = **opiate substitute treatment. †Other than OST medications**

3.4.2 PWID cohort

Almost two-thirds (65%) of the PWID cohort had received opioid substitution therapy (either methadone or buprenorphine +/- naloxone) in the past six months.

In contrast to the POUT participants (Table 5), none of the PWID participants reported having current private health insurance, with 93% reporting that their medical bills were covered by Medicare. The health professionals that PWID most commonly reported seeing in the past month were GP (80%) and opioid substitution therapy doctor (55%). A substantial minority reported also seeing an alcohol counselor and social/welfare worker. The frequency with which PWID saw GPs in the past month was similar to that among POUT participants.

PWID were less likely to report recent emergency health services or hospital admissions compared to POUT participants (Table 5).

Table 5: Recent* health service utilization among the POUT and PWID cohorts

	POUT (n = 108)	PWID (n=133)
Private health insurance%	20.2	0
Medical bills covered (%)		
Medicare	78.0	92.9
Private health insurance	15.6	0
Self/Family	2.8	0.9
Health care access* (%)		
Ambulance	7.4	2.0
Emergency ward	12.0	3.9
Hospital	12.0	0
GP	66.7	80.4
Pain specialist	NA	5.9
Cancer specialist	NA	3.9
Opioid substitution doctor	NA	54.9
Alcohol Counsellor	NA	31.4
Been to hospital as an outpatient	NA	3.9
Specialist doctors	NA	11.8
Dentist	NA	13.7
Psychiatrist	NA	15.7
Psychologist	NA	13.7
Social or welfare worker	NA	29.4
Any other doctors	NA	3.9
Other health professionals	NA	9.8
Mean GP visits (SD)*	1.4 (1.5)	1.8 (1.5)

NA = not askedNote: * = in the last month.

3.5 Illicit drug and alcohol use

3.5.1 POUT cohort

Just over half of the POUT cohort (55%) reported using any illicit drug in the past 12 months, with just over one third (35%) reporting using an illicit drug other than cannabis (Table 6). Most of the POUT cohort (73%) was currently smoking nicotine. In the past 12 months use of heroin (17%), methamphetamine (26%), cocaine (8%) ecstasy (7%) and hallucinogens (5%) was reported by a minority of the sample (Table 6).

3.5.2 PWID cohort

Illicit substance use was common among the PWID, with nearly all participants (99%) reporting recent use of illicit drugs. The illicit substances most commonly used among the PWID cohort in the past six months included heroin (93%), cannabis (76%) and methamphetamine (72%) (Table 6). Alcohol use was also common in the cohort 65%. On average in the past month, PWID participants were using heroin and cannabis every other day, and alcohol and methamphetamine weekly or more frequently (Table 7).

Lifetime overdose was more common among PWID (69%) than POUT participants (54%), with PWID participants reporting (on average) overdosing on 6 occasions in their lifetime (Table 6).

Table 6: Illicit drug and alcohol use at baseline

(%)	POUT (n = 108)	PWID (n=133)
Heroin		
Ever taken	56.5	97.7
Recent use^	16.7	93.5
Methamphetamine		
Ever taken	71.3	88.0
Recent use^	25.9	71.7
Cocaine		
Ever taken	61.1	84.2
Recent use^	8.3	41.9
Ecstasy		
Ever taken	60.2	NA
Recent use^	7.4	NA
Cannabis		
Ever taken	85.2	95.5
Recent use^	41.7	76.0
Alcohol		
Ever taken	99.1	97.7
Recent use^	61.1	64.6
Tobacco		
Ever taken	91.7	NA
Recent use^	73.1	NA
Hallucinogens		
Ever taken	50.9	NA
Recent use^	5.6	NA
Any recent^ illicit drug use, excluding cannabis	35	99.2
Any recent^ illicit drug use, including cannabis	55	99.2
Injected any drug (lifetime)	58.3	100
Ever overdosed	53.7	69.3
Mean # overdoses in lifetime (SD)	1.87 (3.59)	5.6 (18.8)

^'Recent' = past six months for PWID and past 12 months for POUT

Table 7: Frequency of past month illicit drug and alcohol use among POUT and PWID cohorts at baseline

	POUT n=108			PWID n=133		
	Median no. days used past month	Range (min-max)	n	Median no. days used past month*	Range (min-max)	n (who commented)
Heroin	3	1-24	9	16	0-30	115
Methamphetamine	3.5	1-14	10	4	0-30	81
Cocaine	1	1	3	0	0-30	39
Cannabis	12.5	1-30	32	16	0-30	98
Alcohol	4	1-30	46	4.5	0-30	84

*** PWID data calculated as average monthly days used based on days used in the past 6 months**

3.6 Baseline levels of medical and extra-medical use of opioids

3.6.1 POUT cohort

All participants in the POUT cohort had been prescribed an opioid in the past 12 months. Buprenorphine, methadone, codeine and oxycodone were the most commonly reported opioids that were recently (past 12 months) prescribed (Table 8, and Appendix 2 for more detail).

Past 12 month use of non-prescribed (diverted) prescription opioids was less frequently reported than prescribed use for all opioids examined, with the exception of hydromorphone.

3.5.2 PWID cohort

The majority of PWID (86%) had used a pharmaceutical opioid (either their own or someone else's) in the past six months, and 46% of PWID reported recently injecting them. Most commonly, participants reported using an OST opioid (i.e. methadone or buprenorphine+/-naloxone; 79% recent use, 38% recent injection), with half (50%) reporting recent use of a non-OST opioid (36% recent injection).

The opioids most often prescribed to the PWID cohort in the past six months included methadone liquid (63%), codeine (15%) and buprenorphine+/- naloxone (13%) (Table 8). Use of diverted medication was reported by a substantial minority of PWID, with PWID more commonly reporting use of diverted oxycodone (28%), methadone liquid (22%) and morphine (21%).

Table 8: Use of opioid medications at baseline

	POUT	PWID
Morphine* (%)		
Ever prescribed	66.7	26.7
Recent prescribed use	13.0	3.0
Recent non-prescribed (diverted) use	11.1	16.7
Oxycodone* (%)		
Ever prescribed	79.6	24.2
Recent prescribed use	32.4	2.9
Recent non-prescribed (diverted) use	23.1	27.8
Methadone liquid (%)		
Ever prescribed	37.0	85.5
Recent prescribed use	41.7	63.3
Recent non-prescribed (diverted) use	12.0	21.7
Methadone tablets (%)		
Ever prescribed	26.9	22.7
Recent prescribed use	4.6	1.5
Recent non-prescribed (diverted) use	4.6	0
Buprenorphine/naloxone film/tablets (%)		
Ever prescribed	31.5	45.0
Recent prescribed use	43.5	12.0
Recent non-prescribed (diverted) use	3.7	9.2
Buprenorphine patches (%)		
Ever prescribed	16.7	NA
Recent prescribed use	9.3	NA
Recent non-prescribed (diverted) use	2.8	NA
Fentanyl (%)		
Ever prescribed	27.8	5.3
Recent prescribed use	8.3	0
Recent non-prescribed (diverted) use	9.3	0.8
Tramadol* (%)		
Ever prescribed	61.1	NA
Recent prescribed use	14.8	NA
Recent non-prescribed (diverted) use	0.9	NA
Hydromorphone* (%)		
Ever prescribed	16.7	NA
Recent prescribed use	2.8	NA
Recent non-prescribed (diverted) use	5.6	NA
Codeine (%)		
Ever prescribed	88.9	72.5
Recent prescribed use	43.5	14.6
Recent non-prescribed (diverted) use	23.1	4.2
Used OTC codeine products	NA	51.5
Recently used OTC codeine products	31.5#	9.9

NA- Not asked, Note: * = either slow or immediate release. 'Recent'/'recently' = past 12 months for POUT participants, and past 6 months for PWID participants, #recent = past month

The opioid medications most commonly injected by the PWID cohort included methadone (29%), oxycodone (24%), morphine (17%), buprenorphine+/-naloxone (12%) and fentanyl (7%). Codeine injection was reported by one participant. Whereas 28% of PWID cohort participants reported injecting methadone on a weekly or more frequent basis (defined as injection on 24 or more days out of the past 180 days), weekly or more frequent injection of oxycodone and morphine was less common (reported by 9% and 3% of the cohort respectively). In general, the use and injection of non-OST opioids was less common and more sporadic (Table 9).

Table 9: Median days of use and injection of pharmaceutical opioids in the past 6 months among PWID cohort participants

	Median no. days used/injected	Range (min-max)	n
Methadone liquid			
Any use	180	1-180	82
Prescribed use	180	7-180	76
Diverted use	15	1-180	23
Injected	22.5	1-180	26
Methadone tablets			
Any	12.5	11-14	2
Prescribed	12.5	11-14	2
Diverted	0	0-0	0
Injected	0	0-0	0
Buprenorphine (tablets)			
Any	25	1-180	21
Prescribed	60	1-180	10
Diverted	24.5	1-180	16
Injected	19.5	1-180	12
Buprenorphine-naloxone (tablets or film)			
Any	29.5	1-114	16
Prescribed	72	14-100	9
Diverted	9	1-28	10
Injected	3.9	1-73	9
Morphine			
Any	4.5	1-90	24
Prescribed	6.5	1-45	4
Diverted	3.5	1-90	22
Injected	3.0	1-90	25
Oxycodone			
Any	8	1-180	39
Prescribed	14	2-30	3
Diverted	6	1-180	37
Injected	7	1-180	35
Fentanyl			
Any	1	1-1	1
Prescribed	0	0-0	0
Diverted	1	1-1	1
Injected	2.5	1-60	8

3.7 Baseline levels of medical and extra-medical use of other prescription medications

3.7.1 POUT cohort

At baseline, the majority of the cohort (88.9%), reported that they had previously used benzodiazepines (see Table 10). Over one third of the cohort reported that they had used benzodiazepines in the previous month. Of those who had used benzodiazepines in the past month, 11.6% reported that they had used more than one types of benzodiazepine. The most frequently reported benzodiazepines used in the previous month were diazepam (79.1%) and alprazolam (25.6%). Less commonly reported benzodiazepines included oxazepam (9.3%), temazepam (7%), nitrazepam (2.3%), lorazepam (2.3%) and clonazepam (2.3%).

Nearly two-thirds (63.9%) of the POUT cohort reported that they had ever used anti-depressants and 38% reported that they had used them in the previous month. The most frequently reported antidepressants in the past month were mirtazapine (25%), fluoxetine (11.4%), sertraline (11.4%) and duloxetine (9.1%) . Of people who had taken antidepressants within the last month, 4.5% could not remember the brand or type.

One third of the cohort reported that they had experience taking antipsychotic medication at least once in their life time and 17.6% of the cohort reported that they had taken antipsychotic medication within the last month. Of the participants who reported using antipsychotic in the past month, most (84.2%, n = 16) reported that they had taken quetiapine. Less common antipsychotic medications included olanzapine (n = 2), such as Zyprexa (10.5%, n = 2), and paliperidone (Inveda®, n = 1).

3.5.2 PWID cohort

Overall, the levels of other prescription medication use among the PWID cohort were lower than those observed among POUT participants (Table 10). Recent (past month) benzodiazepine use was most commonly reported (23%), followed by anti-depressants (14%) and antipsychotics (8%). The PWID participants who reported using these medications in the past month were taking them close to daily.

Table 10: The use of other prescription medications at baseline

	POUT (n = 108)	PWID (n=133)
Benzodiazepines		
Ever taken (%)	88.9	63.6
Taken in the last month (%)	37.0	23.3
Median days taken in the last month (range)	15.0	24 (1-30)
Anti-depressants		
Ever taken	63.9	43.2
Taken in the last month (%)	38	13.5
Median days taken in the last month (range)	28.0	30 (6-30)
Anti-psychotics		
Ever taken (%)	33.3	25.8
Taken in the last month (%)	17.6	8.3
Median days taken in the last month (range)	28.0	30 (2-30)
Anti-convulsants		
Ever taken (%)	11.1	3.0
Taken in the last month (%)	1.9	0
Median days taken in the last month (range)	28.0	N/A

Note: ** = only includes cases that reported injection history. Recently = past month for POUT participants and past 6 months for PWID participants.

3.7. Differences in the POUT cohort according to history of injecting drug use

Those with a history of injecting differed to those that did not report previous injection in a number of ways; those reporting a history of injection were more likely to be male, were less likely to have current chronic pain and less likely to have current employment. Those with an injecting history were also more likely to have previously to have used illicit drugs and non-prescribed prescription medications, and to be currently using nicotine, cannabis and benzodiazepines (See Table 11).

Table 11: Comparisons between participants that injecting any drug in the past year compared to those that did not report injecting (POUT cohort)

	Injected (n=63)	Not Injected (n=45)	p
Mean Age	39.78(10.25)	41.89(10.93)	.307
Male (%)	**58.7**	**33.3**	**.011**
Employed (%)	**19.0**	**40.0**	**.028**
Current Chronic Pain	**28.6**	**51.1**	**.017**
Mental health			
Moderate to Severe Depression (%)	49.2	55.6	.562
Moderate to severe Anxiety (%)	42.9	33.3	.423
Post-Traumatic Stress Disorder (%)	34.5	35.7	.899
Ever had suicidal thoughts (%)	61.9	56.8	.597
Past 12 month Suicidal thoughts (%)	31.7	24.4	.518
Childhood Maltreatment			
Physical (%)	47.6	48.9	.782
Sexual (%)	38.1	42.2	.579
Emotional (%)	60.3	68.9	.256
Neglect (%)	37.1	37.2	.991
Lifetime overdosed history (%)	58.7	46.7	.215
Mean Sleep Problems Index II score	41.17 (23.19)	44.32 (24.74)	.503
Mean hours slept overnight	7.19 (2.74)	6.70 (1.88)	.310
Past month Health Care Access			
Ambulance (%)	9.5	4.4	.465
Emergency ward (%)	17.5	8.9	.265
Hospital (%)	19.0	11.1	.298
Mean GP visits (SD)*	1.22(1.36)	1.62(1.57)	.161
Substance Use History			
Ever taken heroin	**87.3**	**13.6**	**<.001**
Ever taken methamphetamine (%)	**90.5**	**45.5**	**<.001**
Ever taken cocaine (%)	**77.8**	**38.6**	**<.001**
Ever taken ecstasy (%)	**71.4**	**45.5**	**.007**
Ever taken cannabis (%)	**96.8**	**70.5**	**<.001**
Ever taken hallucinogens (%)	**61.9**	**36.4**	**.011**
Ever taken non- prescr. benzos (%)	**61.9**	**15.9**	**<.001**
Ever taken non-prescr. opioids (%)	**81.0**	**31.8**	**<.001**
Past Month Heroin (%)	**14.3**	**0**	**.010**
Past month Alcohol (%)	49.2	33.3	.117
Past month methamphetamine (%)	39.1	20.0	.437
Past month cannabis (%)	**39.7**	**15.6**	**.010**
Past month nicotine (%)	**82.5**	**55.6**	**.003**
Past month non-prescribed benzodiazepines (%)	**19.0**	**4.4**	**.039**
Aberrant behaviours (1 or more) (%)	59.3	67.4	.417
Mean aberrant behaviours (SD)	4.49 (6.00)	2.77 (4.09)	.107
Dissatisfaction with life (%)	22.2	29.5	.391
Dissatisfaction with health (%)	34.9	43.2	.387

3.8. Differences in the POUT cohort by geographic location

Those living in major cities appeared to have higher levels of employment, current cannabis use and were less likely to report histories of injection drug or heroin use at baseline.

Table 12: Comparisons between those living in Major Cities and Regional/Remote locations (POUT cohort)

	Major City (n = 66)	Regional/Remote (n =42)	p
Mean Age (SD)	39.85 (9.93)	41.93 (11.44)	.320
Male (%)	54.5	47.6	.555
Employed (%)	**36.4**	**14.3**	**.015**
Current Chronic Pain	37.9	38.1	.982
Mental Health			
Moderate to Severe Depression (%)	51.5	52.4	1.000
Moderate to Severe Anxiety (%)	39.4	38.1	1.000
Post-Traumatic Stress Disorder (%)	34.4	35.9	.880
Ever had Suicide thoughts (%)	58.5	61.9	.840
Past 12 month suicidal thoughts (%)	31.8	23.8	.393
Childhood maltreatment			
Physical (%)	53.1	43.9	.425
Sexual (%)	39.1	43.9	.623
Emotional (%)	**73.4**	**53.7**	**.037**
Neglect (%)	37.5	36.6	1.000
Lifetime overdosed history (%)	51.5	57.1	.693
Mean Sleep Problems Index II score	43.28 (22.76)	41.22 (25.49)	.664
Mean hours slept overnight	6.82 (2.51)	7.26 (2.28)	.355
Past month Health Care Access			
Ambulance (%)	7.6	7.1	.933
Emergency ward (%)	18.2	7.1	.154
Hospital (%)	15.2	16.7	.833
Mean GP visits (SD)	1.36 (1.47)	1.43 (1.45)	.823
Substance Use			
Ever taken heroin (%)	**46.2**	**73.8**	**.005**
Ever taken methamphetamine (%)	67.7	78.6	.273
Ever taken cocaine (%)	63.1	59.5	.712
Ever taken ecstasy (%)	64.6	54.8	.308
Ever taken cannabis (%)	83.1	90.5	.395
Ever taken hallucinogens (%)	49.2	54.8	.692
Ever used alcohol (%)	96.9	97.6	1.000
Ever taken non- prescribed benzodiazepines (%)	36.9	52.4	.115
Ever taken non- prescribed opioids (%)	53.8	71.4	.104
Past month Heroin (%)	9.1	7.1	.721

Past month Alcohol (%)	43.9	40.5	.842
Past month cannabis (%)	**45.2**	**19.7**	**.005**
Ever Injected (%)	**50.0**	**71.4**	**.030**
Aberrant behaviours (1 or more) (%)	**73.4**	**44.7**	**.004**
Mean aberrant behaviours	4.02 (4.98)	3.34 (5.91)	.540
Dissatisfaction with life (%)	27.7	21.4	.503
Dissatisfaction with health (%)	44.6	28.6	.108

* someone else's, BZD = Benzodiazepines

4.0 TRAJECTORIES OF OPIOID USE

4.1 POUT cohort

4.1.1 Opioid Use Initiation

The most common reason the POUT cohort reported starting to use pharmaceutical opioids was to relieve physical pain (65.7%), followed by 'to get high/euphoria' (13%). Less common reasons were peer pressure/experimentation (5.6%), to relieve sad or depressed feelings (5.6%), to relieve nervousness/anxiety (3.7%), to substitute for illicit opioids (3.7%) or to counter the effect of other drugs (1.9%).

4.1.2 Reasons for continued opioid use

Reasons for continuing opioids were primarily to avoid withdrawal (41.7%), with fewer continuing opioids for physical pain relief (27.8%), and to get high/euphoria (14.8%) Small numbers again reported other reasons including relieving sad or depressed feelings(5.6%) or nervousness/anxiety (1.9%), to feel normal/better (2.8%).

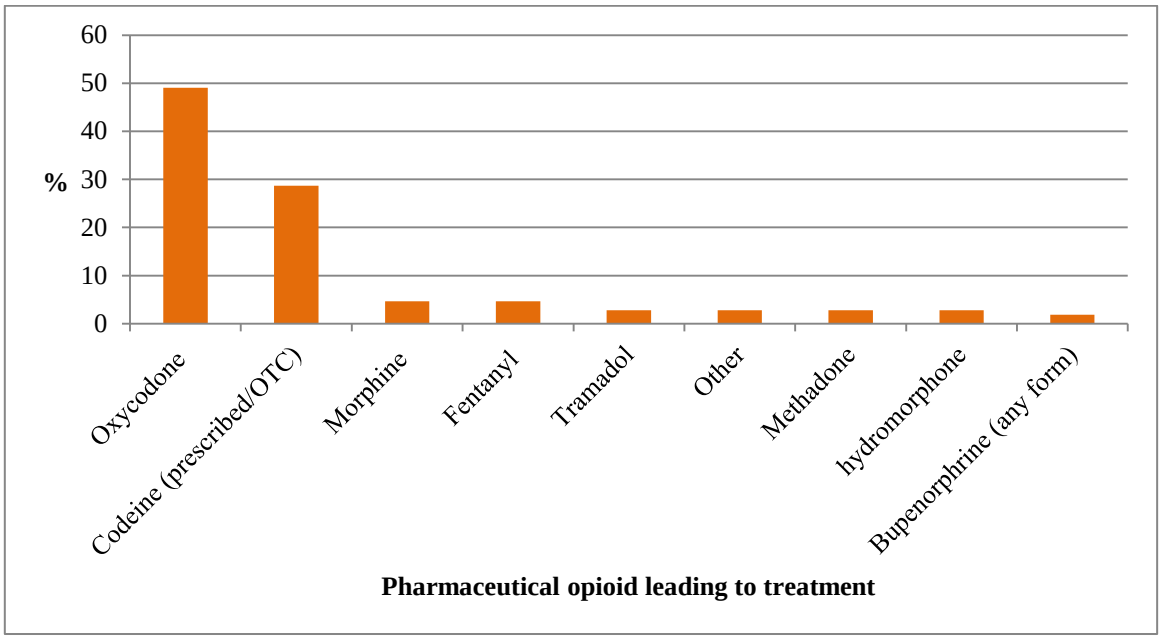
4.1.3 First opioid use non-medically

For those that reported using both heroin and pharmaceutical opioids non-medically (n = 56), for half (n = 28, 50%) heroin use typically preceded pharmaceutical opioid use. There was a small group (n = 8, 14%) that reported commencing pharmaceutical opioid misuse prior to heroin use, a slightly larger group that commenced both in the same year (n = 20, 36%). Three participants specifically identified their initiation of heroin use as the reason that they sought treatment for their PO dependence.

4.1.4 Opioid leading to treatment

The most common opioid that lead to treatment was oxycodone reported by almost half (49%) of the sample (see Figure 1), followed by codeine (29%). Five or less people reported each of the other opioids.

Figure 1 - Main drug leading to treatment in POUT cohort



4.1.5. Correlates of seeking treatment for prescription opioid problems among the POUT cohort

Those entering treatment where the main drug of concern was an OTC medication (representing OTC codeine) appeared generally to be a less complex group with higher levels of employment, less current depression and chronic pain, less illicit substance use and injection history and lower scores for sleep problems. The one indicator where this group appeared to have greater risk was on previous overdose history. The most common substances that the OTC group reported as being involved in their last overdose were alcohol (n = 6), OTC codeine (n = 5), and benzodiazepines (n = 4). The most common drugs reported at the time of the last overdose for the prescription opioid group was alcohol (n = 13) heroin (n = 9), benzodiazepines (n = 8) oxycodone (n = 5), morphine (n = 4) and fentanyl (n = 4).

Table 13: Comparisons between those where Over-The-Counter (OTC) and prescribed (Rx) opioids led to treatment entry (POUT cohort)

	OTC Codeine (n = 23)	Rx Opioids (n =85)	p
Mean Age	43.13 (11.13)	39.99 (10.34)	.206
Male (%)	43.5	49.4	.646
Employed (%)	**56.5**	**20.0**	**<.001**
Current Chronic Pain	**17.4**	**43.5**	**.029**
Mental Health			
Moderate to Severe Depression (%)	**30.4**	**57.6**	**.033**
Moderate to Severe Anxiety (%)	26.1	42.4	.228
Post-Traumatic Stress Disorder (%)	27.3	37.2	.456
Ever had Suicide thoughts (%)	60.9	59.5	1.00
Past 12 month suicidal thoughts (%)	17.4	31.8	.205
Childhood Maltreatment			
Physical (%)	59.1	47.0	.346
Sexual (%)	45.5	39.8	.629
Emotional (%)	77.3	62.7	.312
Neglect (%)	45.5	34.9	.364
Lifetime overdosed history (%)	**73.9**	**48.2**	**.035**
Mean Sleep Problems Index II score	**33.62 (21.19)**	**44.89 (23.98)**	**.043**
Mean hours slept overnight	7.22 (2.76	6.93 (2.34)	.615
Past month Health Care Access			
Ambulance (%)	4.3	8.2	1.00
Emergency ward (%)	13.0	14.1	1.00
Hospital (%)	13.0	16.5	1.00
Mean GP visits (SD)	1.39 (1.41)	1.39 (1.48)	.993
Substance Use			
Ever taken heroin (%)	**30.4**	**64.3**	**.005**
Ever taken methamphetamine (%)	56.5	76.2	.063
Ever taken cocaine (%)	47.8	65.5	.123
Ever taken ecstasy (%)	56.5	61.9	.639
Ever taken cannabis (%)	82.6	86.9	.599
Ever taken hallucinogens (%)	43.5	53.6	.482
Ever taken non- prescribed benzodiazepines (%)	43.5	42.9	.957
Ever taken non-prescribed opioids (%)	56.5	61.9	.639
Past month Heroin (%)	0	11	.103
Past month Alcohol (%)	57	39	.128
Past month cannabis (%)	**13**	**34**	**.050**
Past month nicotine (%)	65	73	.468
Ever Injected (%)	**34.8**	**64.7**	**.016**
Aberrant behaviours (1 or more) (%)	63.6	62.5	1.00
Mean aberrant behaviours	2.23 (3.02)	4.19 (5.74)	.127
Dissatisfaction with life (%)	21.7	26.2	.790
Dissatisfaction with health (%)	34.8	39.3	.811

Those that were considered likely to be experiencing iatrogenic dependence (defined as those that reported they started opioids for pain treatment, were receiving opioids from a doctor with a legitimate script when they began to develop dependence and did not report past 12 month illicit substance use) were compared with those that did not meet these criteria. Those who were classed as meeting criteria for likely 'iatrogenic dependence were more likely to report chronic pain, less likely to report suicidal thoughts, less likely to have had a recent (past month) hospital admission and generally reported lower levels of illicit and unsanctioned pharmaceutical substance use (Table 14).

Table 14: Comparisons between participants meeting criteria for likely iatrogenic dependence and those that did not

	Iatrogenic (n=27)	**Not Iatrogenic** (n=81)	**p**
Mean Age	42.67 (10.18)	39.99 (10.63)	.256
Male (%)	48.1	48.1	1.00
Employed (%)	29.6	27.2	.804
Current Chronic Pain	**59.3**	**30.9**	**.008**
Mental Health			
Moderate to Severe Depression (%)	63.0	48.1	.266
Moderate to severe Anxiety (%)	37.0	39.5	1.00
Post-Traumatic Stress Disorder (%)	36.0	34.7	.904
Ever had Suicide thoughts (%)	**38.5**	**66.7**	**.020**
Past 12 month suicidal thoughts (%)	22.2	30.9	.468
Childhood maltreatment			
Physical (%)	46.2	50.6	.822
Sexual (%)	38.5	41.8	.821
Emotional (%)	65.4	65.8	.967
Neglect (%)	26.9	40.5	.249
Lifetime overdosed history (%)	40.7	58.0	.127
Mean Sleep Problems Index II score	48.02 (25.39)	40.69 (23.11)	.172
Mean hours slept overnight	6.65 (2.31)	7.10 (2.46)	.418
Past month Health Care Access			
Ambulance (%)	0	9.9	.197
Emergency ward (%)	11.1	14.8	.757
Hospital (%)	**0**	**21.0**	**.006**
Mean GP visits (SD)	1.59 (1.37)	1.32(1.49)	.386
Substance Use History			
Ever taken heroin (%)	**26.9**	**66.7**	**<.001**
Ever taken methamphetamine (%)	**50.0**	**79.0**	**.004**
Ever taken cocaine (%)	50.0	65.4	.159
Ever taken ecstasy (%)	**42.3**	**66.7**	**.027**
Ever taken cannabis (%)	**65.4**	**92.6**	**.002**
Ever taken hallucinogens (%)	42.3	54.3	.368
Ever used alcohol (%)	**88.5**	**100**	**.013**
Ever taken non- prescribed benzodiazepines (%)	**7.7**	**54.3**	**<.001**
Ever taken non-prescribed opioids (%)	**19.2**	**74.1**	**<.001**
Ever taken prescribed opioids non-medicinally (%)	**38.5**	**76.5**	**<.001**
Aberrant behaviours (1 or more) (%)	61.5	63.2	.883
Mean aberrant behaviours	3.15 (5.19)	3.97 (5.39)	.501
Dissatisfaction with life (%)	30.8	23.5	.455
Dissatisfaction with health (%)	46.2	35.8	.345

4.1.6 Changes in unsanctioned opioid use from baseline to 3 months

Mean days of non-medical, or diverted (someone else's) opioid use was relatively low and stable when compared between baseline and the three month interview, with a mean of 1 day of unsanctioned opioid use per month at baseline and the three month follow-up.

When only those that had entered treatment in the previous 6 months were compared (n = 39), a significant reduction in unsanctioned opioid use was detected. For non-medical use of own prescribed opioids there was a reduction from a mean of 3.2 (S.D 7.5) days at baseline, reducing to a mean of 0.2 (S.D. 0.9) days in the past month at the three month interview ($p = .017$). A reduction was also observed in the use of diverted opioid medication from 2.7 (S.D. 7.4) days at baseline to 0.2 (S.D. 0.6) days at the three month interview ($p = .042$).

4.2 PWID cohort

4.2.1. Initiation of pharmaceutical opioid use

The vast majority of PWID cohort participants reported having used heroin prior to the onset of pharmaceutical opioid use, with n=5 reported initiating the use of pharmaceutical opioids prior to heroin use.

4.2.2. Correlates of pharmaceutical opioid injection: Are there differences between people who inject pharmaceutical opioids and other PWID?

Table 15(below) compares the baseline characteristics of the PWID cohort participants who reported recent (past six months) injection of pharmaceutical opioids (n=62) compared to the rest of the sample (n=72). PWID who reported recent injection of pharmaceutical opioids were significantly younger, more likely to report recent methamphetamine use and were more likely to be prescribed a (non-OST) opioid medication. There were no differences in gender, other drug use (including heroin), OST utilisation, pain, or number of mental/physical health problems.

Table 15: Comparison of PWID participants who reported recent injection of pharmaceutical opioids with the rest of the sample (baseline data).

	Total sample	**A. Other PWID**	**B. Recent pharm. opioid injectors**	**A vs. B**
	N=133	**n=71**	**n=62**	**(*p*)**
Mean age in years (SD)	40.2 (9.6)	**42.0 (9.9)**	**38.0 (8.8)**	**.02**
Male (%)	60	62	59	.72
Recent^ substance use (%):				
Heroin	87	86	89	.80
Methamphetamine	**60**	**52**	**72**	**.03**
Cocaine	30	21	34	.34
Benzodiazepines	67	61	74	.14
Prescribed opioids^(%)	**66**	**57**	**77**	**.03**
Prescribed an OST medication^ (%)	65	59	72	.14
Median # mental health problems, past year	2 (0-8)	2 (0-8)	2 (0-7)	.76
Median # physical health problems, past year	1 (0-6)	1 (0-6)	1 (0-6)	.66
Current (non-everyday) pain (%)	31	28	34	.45

^= past six months;

4.2.3. Changes in opioid use from Wave 1 to Wave 2

Of the 43 PWID injecting PO at baseline, 53% continued injecting (i.e. injection at both Wave 1 and Wave 2; 28% of the whole sample) and 47% remitted (i.e. injected at Wave 1 but not at Wave 2; 21% of the whole sample). Incident pharmaceutical opioid injection was reported by 7% of PWID. There were no changes in the prescribing of OST and other opioids and patterns of pharmaceutical opioid or heroin injection from Wave 1 to Wave 2, with the exception of lower levels of oxycodone inject at Wave 2 (Table 16 below).

Table 16: Changes in pharmaceutical opioid use and injection among PWID cohort from Wave 1 to Wave 2 (N=100)

	Wave 1 % (95% CI)	**Wave 2 % (95% CI)**
Prescribed an OST opioid^	65 (56-74)	73 (64-82)
Prescribed a (non-OST) pharm opioid^	34 (25-43)	24 (16-32)
Injected a pharmaceutical opioid^	24 (16-32)	36 (27-45)
Any recent^ injection		
Heroin	92 (87-98)	71 (62-80)
Methadone syrup	28 (19-37)	20 (12-28)
Buprenorphine	11(5-17)	4 (0-8)
Buprenorphine-naloxone	7 (2-12)	5 (1-9)
Morphine	17 (10-24)	7 (2-12)
Oxycodone	**26 (17-35)**	**9 (3-15)***
Fentanyl	4 (0-8)	2 (0-5)
Regular (weekly+) injection^^ (%)		
Heroin	78 (70-86)	52
Methadone syrup	6 (1-11)	7 (2-12)
Buprenorphine	5 (1-9)	2 (0-5)
Buprenorphine-naloxone	2 (0-5)	3 (0-6)
Morphine	3 (0-6)	0
Oxycodone	**8 (3-13)**	**0***
Fentanyl	1 (0-3)	0

p<0.05. ^Past six months at baseline, past three months at Wave 2. ^^Defined as injected on >24/180 days at baseline and >12/90 days at Wave 2

5.0 TRAJECTORIES OF PAIN

5.1 POUT cohort

5.1.1 Correlates of pain among the POUT cohort at baseline

Those with current chronic pain at baseline were older, had more sleep problems, and saw the GP more often that those without current chronic pain. Lower levels of non-prescribed (someone-else's) opioid and benzodiazepine use was reported by those with current chronic pain. Those with current chronic pain also reported lower levels of satisfaction with their health.

Table 17: Comparisons between participants that reported experiencing current chronic pain vs those without (baseline)

	Current chronic pain (n=41)	**Non-pain** (n=67)	**Pain vs non-pain**
Mean Age (SD)	**45.0 (9.6)**	**38.0 (10.3)**	**.001**
Male (%)	58.5	41.8	.114
Employed (%)	22.0	31.3	.377
Mental Health			
Moderate to Severe Depression (%)	61.0	46.3	.167
Moderate to severe Anxiety (%)	39.0	38.8	.982
Post-Traumatic Stress Disorder (%)	39.5	32.3	.463
Ever had Suicide thoughts (%)	57.5	61.2	.706
Past 12 month suicidal thoughts (%)	36.6	23.9	.157
Childhood maltreatment			
Physical (%)	59.0	43.9	.137
Sexual (%)	38.5	42.4	.690
Emotional (%)	71.8	62.1	.313
Neglect (%)	41.0	34.8	
Lifetime overdosed history (%)	46.3	58.2	.230
Mean Sleep Problems Index II score	**53.1 (22.9)**	**36.1 (22.1)**	**< .001**
Mean hours slept overnight	6.70 (2.52)	7.16 (2.37)	.340
Past month Health Care Access			
Ambulance (%)	7.3	7.5	1.00
Emergency ward (%)	14.6	13.4	.861
Hospital (%)	19.5	13.4	.400
Mean GP visits (SD)	**1.8 (1.4)**	**1.2 (1.4)**	**.028**
Substance Use History			
Ever taken heroin (%)	50.0	61.2	.258
Ever taken methamphetamine (%)	67.5	74.6	.427
Ever taken cocaine (%)	67.5	58.2	.413
Ever taken ecstasy (%)	62.5	59.7	.839

Ever taken cannabis (%)	82.5	88.1	.423
Ever taken hallucinogens (%)	62.5	44.8	.109
Ever taken non- prescribed benzodiazepines (%)	**30.0**	**50.7**	**.044**
Ever taken non-prescribed opioids (%)	**47.5**	**68.7**	**.030**
Aberrant behaviours (1 or more) (%)	68.4	59.4	.403
Mean aberrant behaviours	3.74(5.21)	3.78(5.43)	.986
Dissatisfaction with life (%)	27.5	23.9	.677
Dissatisfaction with health (%)	**52.5**	**29.9**	**.020**

5.1.2. Changes in pain from baseline to follow-up

Paired t-tests were used to compare mean pain severity and interference (as measured with the Brief Pain Inventory) for the whole sample at baseline and three month interviews. The mean pain interference score, which measures the amount that pain impacts on daily functioning was lower, demonstrating less interference of pain at the three-month time point (mean = 2.65, S.D. 3.36) as baseline compared with mean = 1.95, S.D. 3.01 at 3 months), t (99) = 2.46, p = .016. The mean pain severity score at the two time points did not change significantly (mean = 1.93, S.D. 2.50 compared with mean = 1.61, S.D. 2.47 at 3 months).

5.2 PWID cohort

5.2.1. Correlates of pain among the PWID cohort at baseline

One in three PWID (32%) reported experiencing current pain (other than everyday types of pain) (Table 18). Those PWID who reported pain were also more likely to report comorbid mental health and physical health problems, and were more likely to report recent benzodiazepine use. There were no differences between those with pain and those without on age, gender, patterns of drug use or current PTSD symptoms.

Table 18: Comparison of PWID participants who reported current pain (other than everyday types of pain) with the rest of the sample (baseline data).

%	Total sample N=133	A. Other PWID n=91	B. Current pain n=43	A vs. B (*p*)
Mean age in years (SD)	40.2 (9.5)	39.1 (9.3)	42.5 (9.9)	0.06
Male	60	60	61	1.00
Recent^ use of:				
Heroin	87	89	83	0.40
Methamphetamine	62	61	63	1.00
Cocaine	30	29	33	0.68
Benzodiazepines	**67**	**60**	**81**	**0.04**
Prescribed opioids^	66	66	68	0.98
Prescribed an OST medication^	65	68	60	0.43
PTSD, past month	41	40	42	1.00
Median # mental health problems, past year	**2 (0-8)**	**2 (0-8)**	**3 (0-8)**	**<0.05**
Median # chronic health problems, past year	**1 (0-6)**	**1 (0-6)**	**2 (0-6)**	**0.00**

^= past six months;

5.2.3. Changes in pain from baseline to follow-up

Using paired tests, pain among PWID remained stable at follow-up: there were no changes in the reporting of current pain, or pain severity or interference (see Table 19).

Table 19: Changes in pain among PWID cohort from Wave 1 to Wave 2 (N=100)

	Wave 1	Wave 2	Sig
% reporting current (non-everyday) pain	32 (24-40)	33 (25-41)	p=1.00
Pain levels among those who reported pain			
Mean BPI pain severity score (SD)	4.7 (1.8)	4.7 (1.8)	p=0.92
Mean BPI pain interference score (SD)	5.7 (2.6)	5.1 (2.3)	p=0.31

6.0 CHANGES IN OTHER CLINICAL OUTCOMES FROM BASELINE TO 3 MONTH INTERVIEWS

6.1 POUT cohort

Almost all (94%, n = 92) of participants that were in treatment at baseline were retained in treatment at the 3 months interview. A small number of participants had completed their treatment by the time of baseline interview (for example, completed a short detoxification episode). Two participants that were completed treatment at the time of the baseline had re-entered treatment by the three month interview.

The most common treatments participants were in at 3 months were buprenorphine +/- naloxone (48%, n = 48), methadone (40%, n = 40) and counselling (33%, n = 33).

Symptoms of anxiety and depression were stable over the two time points (see Table 20). A significant reduction in the proportion attending Accident and Emergency departments was detected was detected at the three month interview (p = .049), with no changes in use of ambulance attendance, hospital admission or GP from baseline to three months (Table 7)

Use of substances other than opioids remained low and stable across the two time points (See Table 20) with the exception of nicotine which was the most frequent substance used, with a trend for reducing use over the three month period (p = .057).

Table 20: Changes from baseline to three month interview (n = 101)

	Baseline	Three-month	p
In treatment	97%	93%	.289
Mental Health			
Anxiety Symptoms (GAD Score)	9.13 (6.55)	8.99 (6.26)	.774
Depressive Symptoms, mean (PHQ Score)	11.34 (SD 7.53	11.50 (SD. 1.55)	.782
Health Service Utilisation			
Ambulance Attendance	7.2%	4%	.344
Accident and Emergency Attendance	14.9%	5.9%	**.049**
Hospital Admission	16.8%	11.9%	.383
GP attendance	67.2%	64.4%	.148
Substance Use (Mean days, whole sample)			
Non-medical use of PO	1.4 (4.9)	1.0 (4.1)	.520
Use of diverted PO	1.2 (4.3)	0.8 (3.3)	.458
Non-medical use of BZD	1.0 (4.1)	0.8 (3.8)	.679
Use of diverted BZD	1.2 (4.1)	0.7 (2.6)	.198
Heroin Use	0.6 (2.9)	0.7 (4.1)	.583
Cannabis Use	4.6 (9.7)	4.2 (9.1)	.643
Methamphetamine Use	0.4 (1.8)	0.5 (2.4)	.335
Alcohol Use	3.8 (7.4)	3.9 (7.1)	.802
Nicotine Use	19.6 (13.8)	18.3 (13.7)	.057

Complete case analyses, i.e. N=101 completed Baseline and three month interviews
PO = Prescribed opioids, BZD = Benzodiazepines

6.2 PWID cohort

Examining changes from Wave 1 to Wave using paired tests, there were lower levels of depression at Wave 2 and fewer people reported recent heroin and methamphetamine use at Wave 2 (Table 21). There were no other significant changes at follow up in anxiety, severity of opioid dependence, health service utilization or other illicit drug use.

Table 21: Other changes in clinical profile among PWID from Wave 1 to Wave 2

	Wave 1	**Wave 2**	***p***
Mental Health			
Anxiety, mean GAD score (SD)	6.3 (5.7)	5.8 (5.9)	0.397
Depression, mean PHQ score (SD)	**10.0 (6.5)**	**8.7 (6.5)**	**0.049**
Severity of opioid dependence, mean SDS score (SD)	6.9 (2.7)	8.1 (3.6)	0.068
Health service utilization, %			
Emergency department attendance	2	5	0.873
Hospital admission	0	0	1.000
GP attendance	81	89	0.332
Recent alcohol and other drug use, %*			
Benzodiazepines	65	59	0.286
Heroin	**85**	**71**	**0.004**
Cannabis	72	71	1.000
Methamphetamine	**58**	**47**	**0.041**
Alcohol	66	62	0.454

Complete case analyses, i.e. N=100 PWID completed Wave 1 and Wave 2 interviews. *Recent = past month for Wave 1 and past 3 months/3 for Wave 2.

6.0 EXPERIENCE AND EXPECTATIONS OF TREATMENT (POUT COHORT)

Participants were asked to describe their experience and expectations of treatment. Participants reported mostly positive experiences, with 42% (n = 45) specifically reporting on their positive experience with treatment, making strong positive statements about the medication itself.

> *I call the Suboxone the wonder strips.*
>
> *When I was prescribed the Suboxone I was blown away, it was magic – it was great*

These positive comments were sometimes in contrast with expectations, or highlighted a general lack of knowledge about treatment options amongst this group of pharmaceutical opioid dependent people.

> *I expected it to be a bit scummier than it was.*
>
> *My expectations were very low, I didn't realise there was anything really helpful out there.*

Ten participants also specifically commented on their positive regard for their doctor or the clinic that they attended.

Some participants with current pain conditions made comments about discomfort attending drug and alcohol services:

> *When I go the clinic I feel bad because a lot of people there are on drugs and when I go there people look at me and I feel uncomfortable, because it's called a drug and alcohol place.*

Eight participants specifically commenting on experiencing stigma or made comments that reflected their own stigma towards other substance users

> *If people find out your on methadone, they treat you differently.*
>
> *I want to be treated as a chronic pain patient and not a 'junkie'*

Twelve participants (11%) made specific comments about their pain, and their treatment with several comments highlighting their experience of treatment (eg Suboxone or methadone) being effective for their pain as well as their opioid dependence:

> *I have had a little pain but it's not real chronic like it was before*

Reducing their dose and coming off treatment was a common theme, specifically noted as a wish or expectation by 13% (n = 14) of the participants.

Negative comments were either about how participants were treated (e.g. experiences of stigma, n = 3), the taste of Suboxone (n = 2), concerns about the restrictive nature of the treatment (n = 5), or comments regarding a lack of confidence in their doctors knowledge about pharmaceutical opioid dependence (n = 6).

Participant comments highlighted the differences in treatment approaches for people who inject opioids, and pharmaceutical opioid users.

What they need to be asking is how many GPs did I have …do you know the safe levels of medications ... not warning me about sharing needles

6.1 Treatment reflections at 3 month interviews

Comments about treatment at the three month interview were consistent with participants' expectations and experiences at baseline. The most common theme was positive treatment experience, with 42 (41%) of participants specifically commenting on having a good experience and 20% making specific positive comments about their health care professionals (e.g. doctor or clinic staff).

Wanting to come off, or finding it difficult to come off treatment medication was mentioned by nine participants with a further 10 reporting that they were currently reducing their dose of methadone or buprenorphine (+/- naloxone) at the three month interview.

Five participants reported challenges with pain management at the three month interview. Stigma (either experienced, or towards other substance dependent people) was reported again at the three month interview (n = 7). Other negative aspects of treatment were identified by a small number of participants which included treatment costs (n = 3) and the restrictive nature of treatment in terms of attendance requirements or need to travel to clinics (n = 4). A further four participants reported that they felt they didn't have enough information before starting treatment, or wanted more information about their treatment currently that they had not been able to get.

7.0 DISCUSSION

This unique study compared and contrasts two diverse groups of pharmaceutical opioid users in New South Wales: people seeking treatment for pharmaceutical opioid dependence (POUT), and people who inject drugs (PWID). These cohorts were interviewed on two occasions, providing the first detailed longitudinal data of this kind.

7.1 Key findings

7.1.1. Similarities and differences in the baseline characteristics of the POUT and PWID cohorts

A key finding was that the clinical profiles were similar across both cohorts, despite the PWID cohort being more actively engaged in inner-city illicit drug markets. In general, both the POUT and PWID cohorts are characterised by marked socio-economic disadvantage, significant physical and mental health comorbidities, significant histories of trauma and abuse, pain and high levels of health service utilization. Reported mental health conditions in this group exceed those expected in the normal population, with the mean mental health functioning well below population norms [16]. Key differences between the cohorts were that a substantial minority of the POUT cohort reported no history of injection drug use, and more than half of the POUT sample were female (more than half the PWID cohort were male), in contrast to previous research studies and administrative data for opioid treatment in Australia more generally which find the majority are males [17, 18].

Different subpopulations were identified among both cohorts, reflecting characteristics identified in Australian studies of pharmaceutical opioid related mortality[4]; high levels of pain were reported by the PWID cohort. Amongst the POUT cohort important sub-groups of participants included those with current chronic pain, who reported more complex physical health problems but being less likely to inject or use unsanctioned prescription medications. Conversely those with injecting history were more likely to be unemployed and report a range of illicit and unsanctioned substance drug use. Those using OTC opioids appeared to less complex presentations (i.e. less physical and mental health co-morbidity and few reporting histories of heroin and/or injection drug use), and may be ideal for less supervised treatment programs as a result. These findings suggest that characteristics such as injection history, pain history, and type of opioid used may be associated with differing treatment needs.

7.1.2. Mental health profiles of the POUT and PWID cohorts

Both the POUT and PWID cohorts reported high levels of depression, anxiety and PTSD at baseline. Given that over half of the POUT cohort and 45% of the PWID cohort reported suicidal ideation and over 30% had attempted suicide, improved access to treatment and follow-up may be a high priority for these groups of patients.

Symptoms of depression and anxiety largely remain unchanged over time in the POUT cohort. Among the POUT cohort receiving treatment for depression, compliance rates were high, with medication taken on an average of 27.9 days per month. This compares favorably with compliance for antidepressants in general where median adherence rates are 63% (Range 39- 97%) [19].

7.1.3. Patterns and trajectories of pharmaceutical opioid use

While there is complex interplay between chronic pain, sleep quality, depression and histories of trauma in the POUT cohort, on the whole it appears that this cohort were able maintain reductions in pharmaceutical opioid use over the time period examined. Planned further follow up of the treatment cohort at the 12 month time-point will provide further information about longer term outcomes in this regard.

Although substantial proportions of PWID reported using pharmaceutical opioids, regular injection was infrequent and use was sporadic. There were few differences in the demographic and clinical profiles of people who inject pharmaceutical opioids versus other PWID. The patterns of pharmaceutical opioid use in the PWID cohort suggested a group of primarily opioid dependent people who inject a range of different opioids (including heroin and pharmaceutical opioids) and methamphetamine. The patterns of pharmaceutical opioid use among the PWID cohort were relative stable from Wave 1 to Wave 2, with the exception of a decrease in the levels of oxycodone injection. This decrease is likely to be related to the introduction of a potentially tamper-resistant formulation of controlled-release oxycodone, marketed as Reformulated OxyContin®.

Reformulated OxyContin® was introduced in Australia in April 2014, and the majority of PWID were recruited to the cohort in the months just prior to this date, resulting in

approximately one-third of the Wave 2 interviews being conducted following the removal of the original OxyContin® product. Although this study was not specifically established to evaluate this new formulation, the tamper-resistant formulation may have resulted in the decrease in levels of oxycodone reported at follow-up. This issue is being examined in a large post-marketing surveillance study, the National Opioid Medication Abuse Deterrence (NOMAD) study being conducted at the National Drug and Alcohol Research Centre, and the details of the study methodology and interim findings have been described elsewhere (see [20, 21]).

7.1.4. Pain among the PWID and POUT cohorts

The majority (85%) of the POUT cohort reported at least one problematic pain condition in the past 12 months, with 4 in 10 reporting current chronic pain. Those with current chronic pain appeared to differ from those without in terms of more severe physical problems, including poorer sleep, but generally less illicit or unsanctioned substance use, possibly reflecting lesser substance use histories amongst those that have developed dependence to opioids through a pain condition.

A substantial minority of the PWID cohort reported experiencing current pain, and this group showed higher levels of comorbidity and benzodiazepine use than other PWID. At follow-up, there were no changes in pain severity and interference levels among those who had pain at baseline. PWID with acute and/or chronic pain present clinical challenges. Prescribers may be reluctant to prescribe opioids for pain relief among PWID due the risk of overdose and concerns about drug-seeking [22, 23]. Other factors can complicate pain treatment in this population, including tolerance to opioids following repeated use (resulting in the need for higher doses to obtain adequate pain relief) and hyperalgesia (where increasing opioid doses leads to increased pain responses) [24, 25]. As with anyone experiencing pain, an individual approach to pain management needs to be adopted, with the development of a treatment plan based on individual needs and circumstances, including drug use histories.

7.2. Treatment outcomes and experiences among the POUT cohort

As reported above, the POUT cohort appears to have complex mental health and physical treatment needs, and histories of significant trauma. Despite this, high treatment

retention over time was observed. Further, indicators of pain, physical and mental health either remain stable over time, while some measures such as pain interference, general mental health and ambulance use improved over time. Comments from this group suggest that their experience of treatment is generally positive, though some unique challenges were identified for pharmaceutical opioid dependent people such as discomfort attending services that are identified for people who use drugs.

Open ended questions provided valuable insight into the expectations and experiences of treatment in this group. Positive experiences outweighed negative ones. Some clients reported a reluctance to increase their dose or frustration at being unable to decrease their dose. High rates of relapse have been demonstrated following short (2-12 week) periods of treatment for pharmaceutical opioids [26] highlighting the need to include education about expected treatment lengths and benefits for pharmaceutical opioid users, especially those without previous treatment experience.

There were some findings of interest amongst the POUT cohort. Firstly, the higher proportion of the cohort receiving buprenorphine (+/- naloxone) compared to methadone. This is in contrast to the broader population of predominantly heroin-dependent opioid substitution treatment patients in NSW, where almost 75% receive methadone pharmacotherapy [27]. Possible reasons for higher uptake of buprenorphine (+/- naloxone) may include the possibility of fewer supervision requirements and a preference for using a partial opioid agonist for the treatment of lower potency opioids such as codeine.

While the POUT study was not intended to make comparisons between treatment types, future studies might inform whether different pharmacotherapies have benefits for specific subpopulations of patients such as those with pain conditions, and also examine reasons for treatment selection in this group. Targeting those with ongoing pain might improve sleep, health satisfaction, and less likelihood for self-medication with benzodiazepines and non-prescribed opioids (this hypothesis needs to be tested prospectively).

7.5. Opportunities for intervention

PWID participants commonly reported seeing a GP (80%) and OST doctor (55%) in the past month, presenting important opportunities for intervention. Some POUT participant comments indicated that they had little knowledge of treatment options for opioid dependence, or how to get treatment. Further research might explore in more detail treatment knowledge among out of treatment pharmaceutical opioid users, or better define links from primary care and treatment models for pharmaceutical opioid dependence.

7.4. Limitations

These studies are subject to a number of limitations. The PWID cohort reported lower levels of treatment utilization and were more difficult to follow-up – therefore, follow-up period was 3-6 months post-baseline interview. Both cohort studies are subject to the limitations of self-report, and no objective measures of treatment/clinical outcomes were undertaken (e.g. urinalysis, third-party reports, etc). Self-report has, however, been found to be sufficiently valid and reliable in studies of people who use pharmaceutical opioids extra-medically [28] and/or use illicit drugs [29]. The small sample sizes for each cohort limit statistical power and generalizability. The PWID cohort were a Sydney-based convenience sample who cannot be taken as representative of PWID who live in rural communities or other jurisdictions where OST coverage and heroin availability may be lower. Similarly, they were recruited on the basis of being regular injectors – although half the PWID cohort were in treatment at baseline, and they cannot be taken as representative of pharmaceutical opioid users in treatment. The POUT cohort only interviewed those who had already successfully entered treatment specifically for their pharmaceutical opioid dependence; this cohort is not able to shed light on outcomes among people who are pharmaceutical opioid dependent and only accessing primary care services. While a range of treatment settings referred participants to the POUT cohort, the majority of participants were receiving opioid substitution treatment, with fewer participants reporting shorter term treatments such as detoxification, meaning sufficient numbers are available to examine treatment types individually. Further, three month treatment outcomes represent a relatively short time in in treatment, with minimal changes expected over this time. Longer-term (12 month) follow up as planned will enable further exploration of outcomes for the POUT cohort. One issue arising from the assessment of current pain severity in both these cohorts is that the data were unable to

clearly distinguish between pain related to opioid withdrawal (or overnight lower methadone levels, etc) and other pain conditions. Despite limitations, these pilot studies have highlighted important themes and added to our understanding of pharmaceutical opioid use, dependence and treatment responses.

7.5 Conclusions

These studies represent the first Australian studies to examine pharmaceutical opioid use in detail in diverse clinical populations. Ongoing monitoring of harms in these cohorts is essential - both cohorts displayed complex clinical profiles. Despite low levels of illicit drug use and injection among POUT cohort participants, this cohort displayed more severe clinical profiles. Despite this, the treatment cohort reported high levels of retention and low levels of substance use at the follow-up interview, and reported genearlly positive treatment expereinces. Mental health interventions for both these cohorts are warranted, with high rates of co-morbidity, histories of trauma and suidicalty. Many PWID cohort participants were engaged with health services and obtained opioids via prescription, presenting opportunity for interventions to improve health and clinical outcomes.

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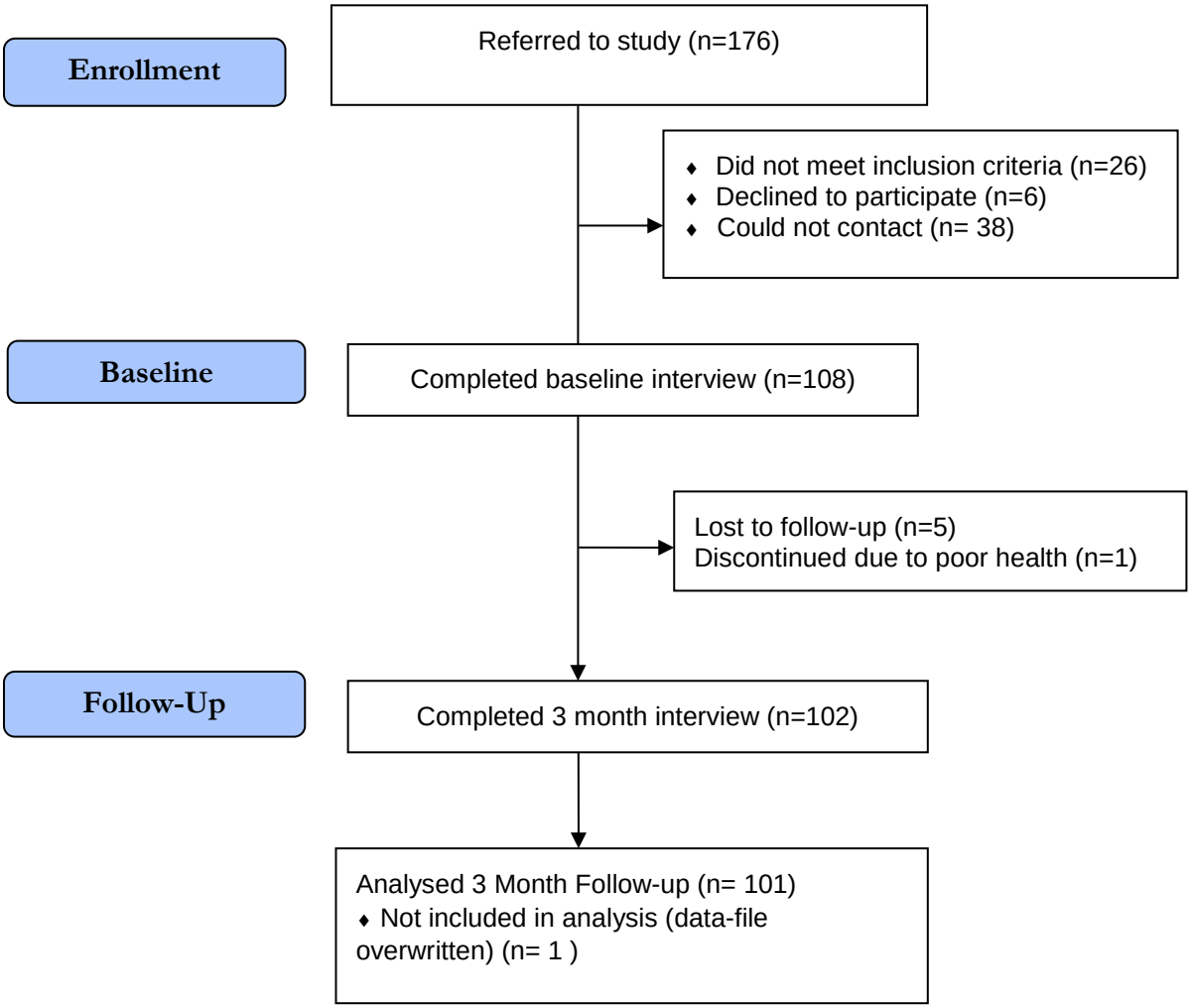
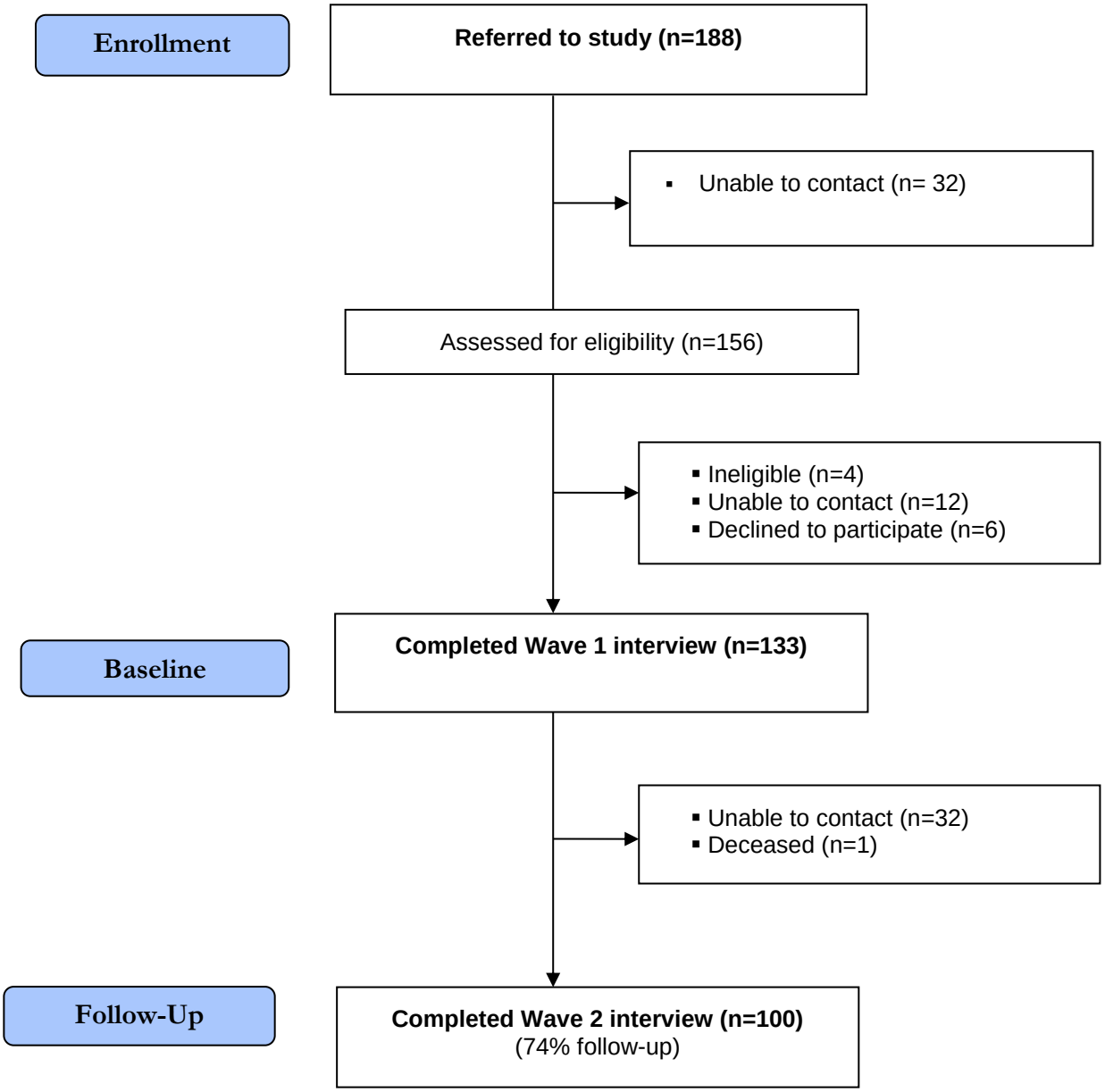
APPENDIX 1: RECRUITMENT FLOWCHARTS

Formation and follow-up of the POUT cohort



Formation and follow-up of the PWID cohort



APPENDIX 2: DETAILED PATTERNS OF PRESCRIPTION OPIOID USE AMONG POUT COHORT PARTICIPANTS AT BASELINE (N = 108)

Prescription Opioid	
Morphine Immediate Release (%)	
Ever Prescribed	50.0
Currently prescribed	0
Used in the last 12 months prescribed	9.3
Used in the last 12 months non-prescribed	5.6
Median day used in the last month (n = 3)	0
Morphine Slow Release (%)	
Ever Prescribed	43.5
Currently prescribed	0.9
Used in the last 12 months prescribed	7.4
Used in the last 12 months non-prescribed	8.3
Median day used in the last month (n = 2)	0
Oxycodone Immediate Release (%)	
Ever Prescribed	65.7
Currently prescribed	0.9
Used in the last 12 months prescribed	24.1
Used in the last 12 months non-prescribed	14.8
Median day used in the last month (n = 4)	1.5
Oxycodone Slow Release (%)	
Ever Prescribed	62.0
Currently prescribed	0.9
Used in the last 12 months prescribed	22.2
Used in the last 12 months non-prescribed	18.5
Median day used in last month (n = 4)	6.0
Methadone Liquid (%)	
Ever Prescribed	58.3
Currently prescribed	37.0
Used in the last 12 months prescribed	41.7
Used in the last 12 months non-prescribed	12.0
Median days used in the last month (n = 42)	30.0
Methadone Tablets (%)	
Ever Prescribed	26.9
Currently prescribed	4.6
Used in the last 12 months prescribed	4.6
Used in the last 12 months non-prescribed	4.6
Median days used in the last month (n = 7)	0.0
Buprenorphine Film/Tablets (%)	
Ever Prescribed	66.7
Currently prescribed	31.5
Used in the last 12 months prescribed	43.5
Used in the last 12 months non-prescribed	3.7
Mean days used in the last month (n = 35)	30
Buprenorphine Patches (%)	
Ever Prescribed	16.7
Currently prescribed	0.9
Used in the last 12 months prescribed	9.3
Used in the last 12 months non-prescribed	2.8
Median days used in the last month (n = 1)	21

Fentanyl (%)	
Ever Prescribed	27.8
Currently prescribed	0.0
Used in the last 12 months prescribed	8.3
Used in the last 12 months non-prescribed	9.3
Median days used in the last month (n = 1)	27.0
Tramadol (any form) (%)	
Ever Prescribed	61.1
Currently prescribed	0.9
Used in the last 12 months prescribed	14.8
Used in the last 12 months non-prescribed	0.9
Median days used in the last month (n = 4)	0
Hydromorphone (any form) (%)	
Ever Prescribed	16.7
Currently prescribed	0.0
Used in the last 12 months prescribed	2.8
Used in the last 12 months non-prescribed	5.6
Median days used in the last month (n = 1)	1.0
Codeine (Prescribed) (%)	
Ever Prescribed	88.9
Currently prescribed	4.6
Used in the last 12 months prescribed	43.5
Used in the last 12 months non-prescribed	23.1
Median days used in the last month (n = 4)	4