Prospective Evaluation

A Typology of Predictive Risk Factors for Non-Adherent Medication-Related Behaviors among Chronic Non-Cancer Pain Patients Prescribed Opioids: A Cohort Study

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Background: There has been no previous prospective examination of the homogeneity of chronic non-cancer pain (CNCP) patients in risk factors for non-adherent opioid use.

Objectives: To identify whether latent risk classes exist among people with CNCP that predict non-adherence with prescribed opioids.

Study Design: Prospective cohort study.

Methods: The Pain and Opioids IN Treatment prospective cohort comprises 1,514 people in Australia prescribed pharmaceutical opioids for CNCP interviewed 3 months apart. Risk factors were assessed in wave 1, and non-adherent behaviors in the 3 months prior to wave 1 and wave 2. Latent class analysis was used to examine groups with differing risk profiles. Logistic regression was used to examine predictors of non-adherence.

Results: A 4-class model was selected with classes described as: 1) Poor Physical Functioning group (27%); 2) Poor Coping/Physical Functioning group (35%); 3) Substance Use Problems group (14%); and 4) Multiple Comorbid Problems group (25%). The latter 2 groups had an increased risk of requesting increased opioid doses, early script renewals, using diverted medication, dose stock-piling, and unsanctioned dose alteration at wave 2.

Limitations: Risk factor onset prior to non-adherent behavior cannot be determined.

Conclusions: Clusters of CNCP patients with distinct risk profiles for non-adherence exist. Each group was identified by at least one risk factor but the likelihood of non-adherent opioid use was higher in groups with particular clusters of multiple risk factors. Not all those with risk factors display non-adherence, emphasising the need for strategies to reduce risk for those patients displaying particular clusters of risks.

Key words: Pain, pharmaceutical opioids, non-adherence, injecting drug use, opioid dependence, chronic non-cancer pain, non-adherence, diversion

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Prescription rates for opioid analgesics have increased in the last 2 decades in the US and globally (1,2), in large part because of increased prescribing for chronic non-cancer pain (CNCP). However, opioid therapy is a controversial primary treatment for CNCP because of its uncertain long-term efficacy and safety (3-5). Associated with increased pharmaceutical opioid use have been increasing rates of overdose and dependence in the US (6-8). The latter have been attributed in large part to non-adherent

opioid (or aberrant) medication-related behaviors (9,10) (defined as those patient practices that fall outside those usually expected in opioid treatment; e.g., diversion, doctor-shopping, and tampering) (11).

Screening tools for predicting risk of non-adherence (12-14) show mixed sensitivity (15). Further, most studies assessing risk factors for non-adherence amongst people with CNCP are retrospective (16-19) and/or use clinical samples treated for substance abuse or chronic pain problems (20,21). Risk factors are often considered in isolation, with limited attention to their relative predictive value or potential interactions between risk factors in different domains in predicting non-adherent opioid medication-related behavior. Although research has shown pain patients can be divided into subgroups (22), there is a lack of prospective research assessing how the people with risk factors for non-adherence cluster, and whether these subgroups predict later problems. There is an important opportunity to better identify those patients at risk of non-adherent medication use to alert clinicians and protect patient health, a task that was identified many years ago (23) and reiterated more recently (24).

Objectives

The decision to prescribe requires a cost-benefit analysis in which potential pain relief is weighed against the likelihood of adverse or unwanted effects for the patients, including non-adherent opioid use (25). Given predicted increased prevalence of CNCP, and current rates of morbidity and mortality associated with CNCP opioid therapy, it is crucial that the predictive utility of potential risk factors for non-adherent opioid use is ascertained. The Pain and Opioids IN Treatment (POINT) study (26) comprises a prospective cohort of 1,514 people prescribed pharmaceutical opioids for CNCP that aims to undertake a large-scale longitudinal assessment of the safety and efficacy of opioid therapy and non-adherent opioid use in persons with CNCP recruited from the general population. As such, the aims of the current study were to:

1. Identify subgroups of people with CNCP based on their risk factors for non-adherent opioid use;
2. Compare the demographic, pain, treatment, and health service access profile of these subgroups; and
3. Assess whether subgroup membership predicted non-adherent opioid use assessed cross-sectionally at recruitment and prospectively over 3 months.

Methods

Study Design, Setting, and Participants

The POINT cohort comprises 1,514 people prescribed opioids for CNCP in Australia. Data were drawn from wave 1 (i.e., time point 1 of data collection) and wave 2 (3 month) interviews (full details of the study design have been published elsewhere [26]). The study was approved by the UNSW Human Research Ethics Committee (#HC12149). The study also received A1 National Pharmacy Guild Approval to approach pharmacists to assist with recruitment (#815).

Inclusion and Exclusion Criteria

Inclusion criteria comprised: i) aged 18 or older, ii) competent in spoken/written/reading English, iii) without apparent memory or other cognitive impairment, v) living with CNCP (defined as pain present daily for a minimum of 3 months), and vi) prescribed a strong opioid (classified within Schedule 8 of the Australian Uniform Scheduling of Medicines and Poisons) (27) for more than 6 weeks at the time of admission in the cohort. Schedule 8 opioids comprise morphine, oxycodone, fentanyl, buprenorphine, methadone, hydromorphone, and codeine phosphate as a single ingredient. Exclusion criteria comprised cases where Schedule 8 opioids were prescribed for opioid substitution therapy (methadone and buprenorphine for opioid dependence) or cancer pain.

Recruitment and Interview Procedures

Participants were recruited through pharmacies. From a database of 5,745 community pharmacies, 1,868 were willing to refer potentially eligible participants (see [28] for further detail). In total, 35% of pharmacies across Australia agreed to participate. Of those who were referred (n = 2,725), 1,873 were eligible, and 1,514 participants completed wave 1. Retention at wave 2 was 80% (n = 1,207), of whom 56% were female; full participant flowchart is available elsewhere (28). Phone interviews at wave 1 were conducted by trained interviewers. Interviewers had a minimum 3-year health or psychology degree. Interviewers received suicide assistance training, and were provided glossaries of general and chronic pain medications and conditions. Interviewer training comprised a day of training in the administration of the clinical interview, followed by mock interviews and for the first 5 interviews they were supervised by the project coordinator to ensure consistency between all interviewers. Overall training was approximately 15 hours. Self-completed questionnaires were completed at wave 2 (paper or online).

Variables and Data Sources/Measurement

Risk Factors for Non-Adherent Behavior (Wave 1)

Risk factors for non-adherent opioid use for people with CNCP were identified via a literature review of tools and guidelines developed to predict risk of non-adherent opioid use and studies identifying predictors of non-adherent opioid use (12-14,16-21,29-50). Authors AP, RB, and LD extracted key risk factors which were then reviewed by all authors. Specific risk factors identified in the literature are summarized in Table 1 along with the method of assessment used for each factor for the current study.

Demographics, Pain Characteristics, Treatment Characteristics, and Health Service Access (Wave 1)

In addition to demographics, participants reported lifetime pain conditions, and pain duration. Participants also completed the Brief Pain Inventory short-form (BPI) (51). Treatment characteristics included the duration (continuous) of current prescribed opioids, and past month opioid and psychiatric prescription medications. Health service utilization was also assessed within this period.

Non-Adherent Opioid Use (Wave 1 and Wave 2)

Participants were asked to report whether they had engaged in 10 behaviors in the preceding 3 months which had been identified as non-adherent in the literature (11). These items comprised: requested an increased opioid dose, early script renewal, diversion, using opioids from non-medical sources, stock-piling, doctor shopping, frequently losing opioid medication, unsanctioned dose alteration, tampering, and non-pain related opioid use.

Statistical Methods

Latent class models (one to 6 classes) were estimated using risk factors for non-adherent opioid use and the fit of each model was compared using MPlus v7 (52). Three criteria were used to assess model fit following standard procedures for LCA model selection (53). Akaike's Information Criterion (AIC) and sample-size adjusted Bayesian Information Criterion (ssaBIC) were used to assess model fit; lower values

Table 1. *Risk factors identified in the literature included in latent class analyses.*

Risk Factor Identified in the Literature (with example sources)	Definition in the Current Study
Personal history of drug and/or alcohol misuse, abuse or dependence (12-14,16,20,29-31,35-39,44-46,49,57)	Lifetime mental and behavioural disorder due to psychoactive substance use (meet International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) criteria assessed via the Composite International Diagnostic Interview (CIDI) (58))
Family history of drug and/or alcohol misuse, abuse or dependence (16,30,35,36,44,49)	Composite International Diagnostic Interview (CIDI) items assessing mother or father problems with alcohol or other drugs(58)
Affective disorder (12,14,19,29-31,35,37,47,57)	Score ≥10 on the Patient Health Questionnaire-9 (PHQ-9)(59,60) Score ≥10 on the Generalised Anxiety Disorder -7 Modules of the Patient Health Questionnaire(61)
Childhood abuse (12,13,17,37)	Any experience of physical, sexual, and/or emotional abuse prior to age 16 based on questions by Sansone (2009)(62)
Post-traumatic stress disorder (PTSD) (12,30,31,37,57)	Score ≥3 on the Primary Care PTSD(63) screen
Significant personality disorder (14,29,31,57)	Screening positive to ICD-10 diagnosis of Borderline Personality Disorder (BPD) using the National Survey of Mental Health and Wellbeing version of the CIDI (64)
Younger age (12,20,21,35,49)	Self-reported age less than 45 years
Problematic physical condition (35)	Any problematic chronic medical condition in the last 12 months, assessed via the Chronic Conditions section of the CIDI(58)
Involvement of multiple body regions (35)	Reporting ≥ 3 of the primary pain conditions (back/neck problems, arthritis/rheumatism, frequent/severe headaches, visceral pain, fibromyalgia, shingles-related pain) from the Chronic Conditions section, CIDI
Functioning below normal expectation (35,38)	Two standard deviations (score=30) below the norm of 50 in the Physical Health subscale of the 12-item Short-Form Health Survey (SF-12) (29)
Poor coping strategies (35)	Score ≤ 30 on the Pain Self-Efficacy Questionnaire (PSEQ) (65,66)
Lack of social support (14,29,30,44)	Average score ≤ 3 on Medical Outcomes Survey (MOS) Social Support

indicated better fit. The Lo-Mendell-Rubin adjusted log-likelihood ratio test (LMR-ALRT) statistic (54) was used to compare fit of a k class model with a *k*-1 class model; $P < .050$ indicated that the latter model should be rejected in favor of the former. Entropy was used as an index of class classification accuracy; higher values (range 0.0 – 1.0) indicated better differentiation of individuals into classes. Class composition of models was examined alongside fit statistics to determine which model had the most parsimonious and meaningful class structure.

The most likely class membership for each participant based on the chosen model was used in subsequent analyses. Demographic, pain characteristics, treatment characteristics, and health service utilization correlates of latent class membership were analyzed using univariate logistic regression conducted in SPSS Statistics v21 (55). Descriptive statistics comprised percentages for categorical data and the median for continuous data with significant skew and/or kurtosis. The Mann Whitney-U test was used for analyses of the latter variables. Multivariate logistic regression were run for non-adherent behavior items, controlling for duration of continuous current prescribed opioid use (wave 1 and wave 2) and wave 1 non-adherence for each specific item (wave 2). Across all analyses, significance levels were maintained at $P < .050$.

Results

Participants

The sample was largely balanced for gender (56% female), and the median age was 58 years (Table 3). The majority had completed tertiary/trade qualifications (65%). However, 49% were unemployed, 31% were retired, and 59% reported a low income comparable with disability/unemployment benefits.

Participants generally had a long history of pain (median 10 years), with 80% reporting chronic back/neck problems, 67% arthritis/rheumatism, 45% severe/frequent headaches, and 33% visceral pain in the past year (Table 3). Participants had a median of 4 continuous years of current prescription opioid use. Past month access of GP {sp} services was common (95%), with lower rates of seeing a physiotherapist (16%) and a medical specialist (15%). Approximately two-fifths reported one or more non-adherent opioid medication-related behaviors at wave 1 (38%) and wave 2 (44%) (Table 4). Asking for an increase in dose (21%) or an early script renewal (12%) were the most commonly reported behaviors.

Latent Class Analysis of Risk Factors for Non-Adherent Opioid Use

Model Selection

Examination of model fit statistics showed that AIC was smallest for the 6-class model, ssaBIC was smallest for the 5- and 6-class model, and entropy was greatest for the 2-class models (Table 2). However, the chi-square test indicated improved model fit for the 4-class model over a 3-class solution; no further improvement was indicated for more complex models. Examination of class composition alongside fit statistics supported selection of the 4-class model: each class was substantive and clearly distinct in their patterns of risk factors.

Table 2. *Latent class fit statistics for POINT predictor models with 1 to 6 classes.*

Model	AIC	ssaBIC	LMR-ALRT	LMR-ALRT *P* value	Entropy	Proportion of Sample in Each Class					
						Class 1	Class 2	Class 3	Class 4	Class 5	Class 6
1 Class						1.00	-	-	-	-	-
2 Class	19236	19289	1111.666	< 0.001	0.672	0.61	0.39	-	-	-	-
3 Class	19126	19207	134.571	0.0305	0.574	0.39	0.29	0.32	-	-	-
4 Class	19011	19120	139.473	0.0117	0.583	0.27	0.35	0.14	0.25	-	-
5 Class	18976	19114	59.537	0.2562	0.600	0.18	0.11	0.21	0.80	0.42	-
6 Class	18949	19114	52.813	0.2575	0.605	0.90	0.31	0.24	0.10	0.90	0.18

Note. AIC: Akaike Information Criterion; ssaBIC: sample-size adjusted Bayesian Information Criterion; LMR-ALRT: Lo-Mendell-Rubin Adjusted Likelihood Ratio Test; POINT: Pain and Opioids in Treatment study

Latent Class Probabilities and Class Definitions

One-quarter (27%) of the sample had a high probability (> 0.5) of reporting poor physical functioning and a low endorsement of substance abuse history, psychiatric problems, poor coping, and low social support (Poor Physical Functioning group). One-third (35%) were identified by poor physical functioning, coupled with a high probability of poor coping strategies, poor social support, and the likelihood of an affective disorder (Poor Coping and Physical Functioning group). Just over one-tenth (14%) had a high probability of personal substance abuse history; this group was more likely to be younger and to have experienced childhood maltreatment (Substance Use Problems group). One-quarter (25%) reported a high probability of personal substance abuse history and experience of child abuse, coupled with a high probability of affective disorder, borderline personality disorder, PTSD, and family substance abuse history, and a high probability of reporting poor functioning, poor coping strategies, and poor social support (Multiple Comorbid Problems group) (Fig.1).

Correlates of Group Membership

The Poor Physical Functioning group served as reference for univariate logistic regression analyses because this group had a low probability of experiencing any of the risk factors for non-adherence with the exception of low functioning. Compared to the Poor Physical Functioning group: i) the Poor Coping and Physical Functioning group were younger and had greater odds of being unemployed and having a low income; ii) the Substance Use Problems group had greater odds of being male, unemployed, and without tertiary qualification, and lower odds of being in a stable relationship and having a low income; and iii) the Multiple Comorbid Problems group were younger and less likely to be in a stable relationship, with 8-fold increased odds of being unemployed (Table 3).

While chronic back/neck problems were predominant in the sample, rates were higher in the Multiple Comorbid Problems group than in the Poor Physical Functioning group. There were lower mean BPI severity and interference scores, lower rates of psychiatric medication use, and lower frequency of mental health professional visits related to pain in the Poor Physical Functioning group than in all others. The Multiple Comorbid Problems group also had significantly greater odds of reporting recent GP visits, emergency department visits, and ambulance attendance than the Poor Physical Functioning group (Table 3).

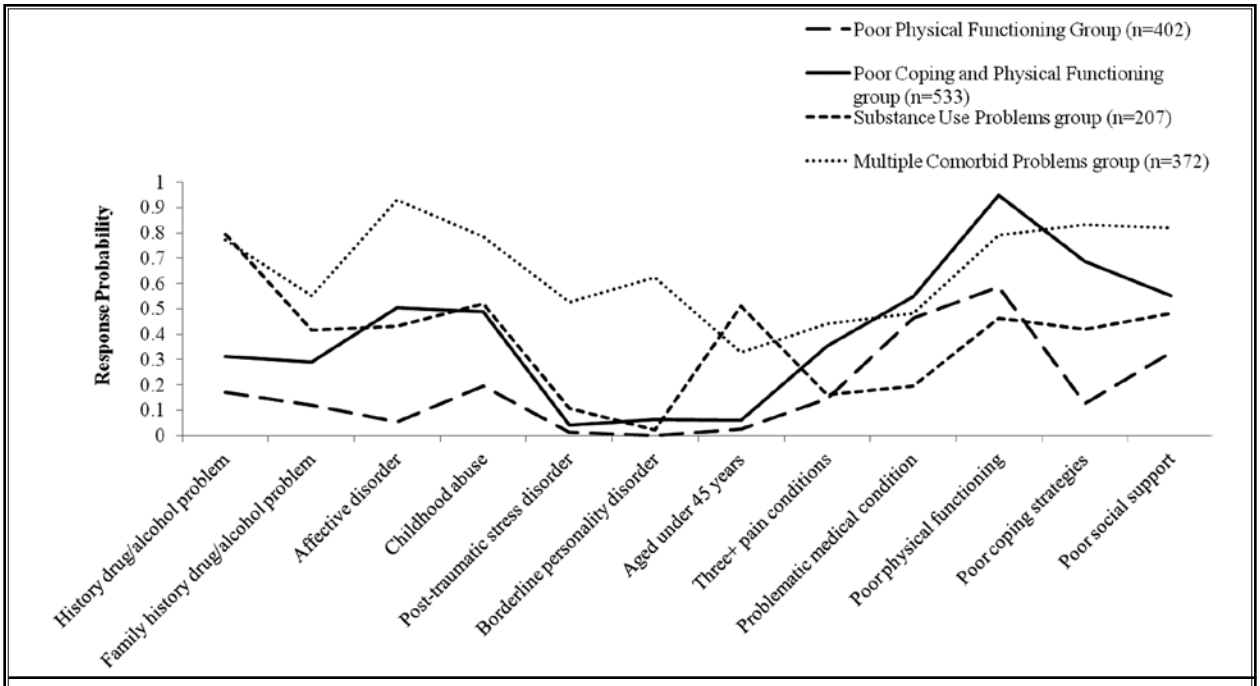

Fig. 1. *Response probabilities according to group for the 4-class solution (n = 1,514).*

Table 3. *Wave 1 correlates of group (n = 1,514).*

Outcome[a]	Total Sample (n = 1,514)	(A) Poor Physical Functioning Group n = 402	(B) Poor Coping and Physical Functioning Group n = 533	(C) Substance Use Problems Group n = 207	(D) Multiple Comorbid Problems Group n = 372	B vs A (ref) b	C vs A (ref) b	D vs A (ref) b
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	OR (95% CI) *P* value	OR (95% CI) *P* value	OR (95% CI) *P* value
Demographics:								
Age (M, IQR)	58 (48-67)	68 (59-75)	60 (53-68)	43 (36-53)	51 (42-58)	Z = -7.98, *P* < .001	Z = -16.66, *P* < .001	Z = -16.42, *P* < .001
% Male	44 (42-47)	44 (39-49)	40 (36-44)	55 (48-62)	46 (41-51)	0.83 (0.64-1.08), *P* = .17	1.56 (1.11-2.18), *P* = .010	1.07 (0.81-1.42), *P* =. 64
% Not completed tertiary education	35 (33-38)	32 (28-37)	35 (31-39)	44 (37-50)	35 (30-40)	1.16 (0.88-152), *P* = .30	1.65 (1.17-2.33), *P* = .001	1.15 (0.85-1.55), *P* = .36
% Unemployed	49 (46-51)	22 (19-27)	51 (47-55)	53 (46-59)	72 (67-76)	3.58 (2.68-4.78), *P* < .001	3.84 (2.68-5.51), *P* < .001	8.91 (6.43-12.34), *P* < .001
% Weekly income < AUD400	59 (56-61)	58 (53-62)	65 (60-69)	49 (42-56)	57 (52-62)	1.35 (1.03-1.76), *P* = .028	0.71 (0.50-0.99), *P* = .042	1.00 (0.75-1.33), *P* = .99
% Married/Defacto	54 (51-56)	62 (57-66)	56 (52-60)	53 (46-59)	43 (38-48)	0.78 (0.60-1.02), *P* =.067	0.69 (0.49-0.97), *P* =.032	0.46 (0.34-0.61), *P* <.001
Pain Characteristics:								
Duration of living in pain (months; M, IQR)	120 (54-240)	120 (52-252)	156 (63-288)	96 (36-168)	120 (55-240)	Z = 1.96, *P* = .049	Z = -3.55, *P* < .001	Z = -0.03, *P* = .98
Pain conditions (lifetime):								
% Chronic back/neck problems	80 (78-82)	76 (71-80)	80 (76-83)	74 (68-80)	86 (82-89)	1.28 (0.94-1.75), *P* = .12	0.94 (0.64-1.38), *P* = .74	2.03 (1.40-2.95), *P* < .001
% Arthritis/ rheumatism	67 (65-69)	73 (69-78)	76 (72-79)	40 (34-47)	63 (58-68)	1.12 (0.84-1.51), *P* = .44	0.24 (0.17-0.35), *P* < .001	0.62 (0.45-0.84), *P* = .002
% Frequent/severe headaches	45 (42-47)	30 (26-35)	46 (42-50)	43 (36-50)	60 (55-65)	1.98 (1.50-2.60), *P* < .001	1.75 (1.24-2.48), *P* = .002	3.52 (2.61-4.73), *P* < .001
% Visceral pain	33 (31-35)	23 (19-27)	37 (33-42)	26 (21-33)	41 (36-46)	2.04 (1.52-2.73), *P* < .001	1.21 (0.82-1.78), *P* = .34	2.39 (1.75-3.26), *P* < .001
Brief Pain Inventory: Severity (M, IQR)	5 (4-6)	5 (3-6)	6 (4-7)	5 (4-6)	6 (5-7)	Z = 7.94, *P* < .001	Z = 3.61, *P* < .001	Z = 10.39, *P* < .001
Brief Pain Inventory: Interference (M, IQR)	6 (4-7)	4 (2-6)	6 (5-8)	6 (4-7)	7 (6-8)	Z = 15.43, *P* < .001	Z = 7.14, *P* < .001	Z = 18.27, *P* < .001
Treatment:								
Current prescribed medication:								
% Morphine	15 (13-17)	11 (9-15)	16 (13-19)	17 (12-23)	17 (14-21)	1.51 (1.02-2.22), *P* = .038	1.61 (1.00-2.60), *P* = .049	1.65 (1.09-2.49), *P* = .017
% Oxycodone	61 (59-64)	52 (47-56)	61 (57-65)	67 (60-73)	69 (26-36)	1.48 (1.14-1.93), *P* = .003	1.88 (1.33-2.67), *P* < .001	2.11 (1.57-2.83), *P* < .001
% Buprenorphine	22 (20-24)	34 (30-39)	21 (18-25)	12 (9-18)	13 (10-17)	0.53 (0.39-0.71), *P* < .001	0.28 (0.18-0.44), *P* < .001	0.29 (0.20-0.42), *P* < .001
% Methadone	4 (3-5)	2 (1-4)	5 (3-7)	6 (3-10)	5 (3-8)	2.78 (1.19-6.49), *P* = .018	3.47 (1.35-8.96), *P* = .010	2.87 (1.18-6.95), *P* = .020
% Fentanyl	15 (13-16)	15 (12-19)	15 (13-19)	13 (9-18)	14 (11-18)	1.04 (0.72-1.49), *P* = .85	0.82 (0.50-1.34), *P* = .43	0.93 (0.62-1.38), *P* = .71
% Tramadol	10 (8-11)	10 (7-13)	8 (6-10)	12 (8-17)	12 (9-16)	0.73 (0.46-1.16), *P* = .19	1.19 (0.69-2.03), *P* = .53	1.21 (0.77-1.91), *P* = .40
% Hydromorphone	4 (3-5)	3 (2-5)	4 (3-6)	4 (2-7)	4 (3-7)	1.46 (0.70-3.06), *P* = .32	1.43 (0.57-3.61), *P* = .45	1.60 (0.73-3.49), *P* = .24

Table 3. *Wave 1 correlates of group (n = 1,514) (continued).*

Outcome[a]	Total Sample (n = 1,514)	(A) Poor Physical Functioning Group n = 402	(B) Poor Coping and Physical Functioning Group n = 533	(C) Substance Use Problems Group n = 207	(D) Multiple Comorbid Problems Group n = 372	B vs A (ref) b	C vs A (ref) b	D vs A (ref) b
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	OR (95% CI) *P* value	OR (95% CI) *P* value	OR (95% CI) *P* value
% Prescription codeine	24 (22-27)	17 (13-21)	24 (21-28)	29 (23-35)	31 (26-36)	1.61 (1.16-2.24), *P* = .004	1.99 (1.34-2.97), *P* = .001	2.21 (1.57-3.11), *P* < .001
% Benzodiazepines	34 (32-36)	20 (16-24)	31 (27-35)	38 (31-45)	52 (47-57)	1.79 (1.32-2.43), *P* < .001	2.43 (1.68-3.53), *P* < .001	4.34 (3.16-5.97), *P* < .001
% Antidepressants	52 (49-54)	34 (30-39)	56 (52-60)	49 (42-56)	66 (61-71)	2.44 (1.87-3.20), *P* < .001	1.82 (1.30-2.57), *P* = .001	3.74 (2.77-5.03), *P* < .001
Duration continuous opioid medication (months; M, IQR)	48 (19-120)	36 (18-108)	60 (24-144)	36 (12-108)	57 (24-120)	Z = 4.06, *P* < .001	Z = -0.49, *P* = .63	Z = 3.00**, *P* = .003
Health Service Access (past month)								
% GP	95 (94-96)	93 (90-95)	96 (94-97)	96 (92-98)	97 (94-98)	1.67 (0.93-2.97), *P* = .084	1.58 (0.73-3.43), *P* = .24	2.16 (1.08-4.33), *P* = .030
% Medical specialist	15 (13-16)	12 (9-16)	16 (13-19)	16 (12-22)	15 (11-19)	1.34 (0.92-1.96), *P* = .13	1.42 (0.88-2.27), *P* = .15	1.23 (0.81-1.86), *P* = .33
% Psychiatrist	4 (4-6)	1 (1-2)	4 (3-6)	3 (1-6)	10 (7-13)	0.824 (1.92-35.33), *P* = .005	5.97 (1.19-29.85), *P* = .030	22.09 (5.29-92.33), *P* < .001
% Psychologist	7 (6-8)	1 (1-3)	6 (5-9)	8 (5-12)	13 (10-16)	5.43 (2.11-14.02), *P* < .001	6.65 (2.40-18.43), *P* < .001	11.52 (4.53-29.30), *P* < .001
% Physiotherapist	16 (14-18)	15 (12-19)	16 (13-19)	16 (11-21)	17 (14-21)	1.11 (0.77-1.59), *P* = .58	1.06 (0.67-1.70), *P* = .80	1.19 (0.81-1.75), *P* = .38
% Emergency medical treatment	12 (11-14)	8 (6-11)	12 (9-15)	12 (8-17)	18 (14-22)	1.45 (0.93-2.27), *P* = .10	1.54 (0.892.66), *P* = .13	2.41 (1.55-3.76), *P* < .001
% Ambulance	7 (6-8)	5 (3-8)	8 (6-11)	3 (2-7)	9 (6-12)	1.56 (0.91-2.68), *P* = .11	0.64 (0.27-1.52), *P* = .31	1.77 (1.00-3.11), *P* = .049

a Tertiary education was defined as completing university or trade qualifications; low income was classified as greater or less than AUD400/week, with less than AUD400/week comparable with Australian unemployment and disability benefits. Note that psychiatrist and psychologist visits were defined as those related to pain. b Univariate logistic regression results are presented here. An odds ratio (OR) of 1 indicates the event is equally probable in each group, > 1 indicates the event is more likely to occur in the non-reference group relative to the reference group, and < 1 indicates the event is less likely to occur in the non-reference group; relative to the reference group. Mann-Whitney U tests were conducted for continuous variables. 95% CI: 95% confidence interview; IQR: interquartile range.

Non-Adherent Opioid Use According to Group

Wave 1

At wave 1, all risk groups had a higher percentage of participants reporting dose-escalation, early script renewal, and stockpiling than the Poor Physical Functioning group, even after controlling for duration of prescription opioid use (Table 1, 4). The Substance Use Problems group also had 3-fold higher odds of unsanctioned dose alteration, 5-fold increased odds of using opioids from non-medical sources, and 9-fold increased odds of using medication for non-pain purposes than the Poor Physical Functioning group. The Multiple Comorbid Problems group also had greater odds of unsanctioned dose alteration, using opioids from non-medical sources, and using medication for non-pain purposes, and a 3-fold higher odds of frequently losing medication/scripts.

All 3 risk groups had a greater number of people reporting one or more non-adherent behaviors at wave 1 than the Poor Physical Functioning group. Odds ratios were calculated to compare non-reference groups. There was a similar rate of participants reporting one or more non-adherent behaviors in the Poor Coping and Physical Functioning group and Substance Use Problems group (OR = 1.34, 95%CI 0.97 – 1.86, *P* = .090), with the Multiple Comorbid Problems group reporting significantly higher rates of non-adherence than the former

Table 4. *Non-adherent opioid use (past 3 months) at Wave 1 (n = 1,514) and Wave 2 (n = 1,201) according to group.*

Non-Adherent Opioid Medication Behavior (past 3 months)a	Total Sample (n = 1,514)	(A) Poor Physical Functioning Group n = 402	(B) Poor Coping and Physical Functioning Group n = 533	(C) Substance Use Problems n = 207	(D) Multiple Comorbid Problems Group n = 372	B vs A (ref) b	C vs A (ref) b	D vs A (ref) b
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	AOR (95% CI) *P* value	AOR (95% CI) *P* value	AOR (95% CI) *P* value
Wave 1								
Asked doctor for an increase in prescribed dose	21 (19-23)	13 (10-16)	21 (18-25)	24 (19-30)	30 (25-35)	1.90 (1.32-2.72), *P* = .001	2.13 (1.38-3.30), *P* = .001	2.96 (2.05-4.29), *P* < .001
Asked doctor for early prescription renewal because I had run out early	12 (11-14)	3 (2-6)	11 (8-14)	20 (15-26)	21 (17-25)	3.51 (1.89-6.52), *P* < .001	7.35 (3.83-14.12), *P* < .001	7.70 (4.19-14.14), *P* < .001
Used another person's opioid medication	2 (2-3)	1 (1-3)	1 (0-2)	6 (3-10)	3 (2-6)	0.73 (0.21-2.56), *P* = .63	5.00 (1.74-14.41), *P* = .003	2.63 (0.92-7.56), *P* = .072
Saved up my opioid medication	8 (7-10)	3 (2-6)	6 (5-9)	11 (7-16)	14 (11-18)	1.99 (1.04-3.83), *P* = .094	3.65 (1.80-7.41), *P* = .001	4.75 (2.54-8.90), *P* < .001
Gone to a different doctor to get more opioid medication and didn't tell my normal doctor	1 (1-2)	1 (0-2)	1 (0-2)	2 (1-4)	2 (1-4)	0.98 (0.16-5.94), *P* = .98	3.21 (0.53-19.45), *P* = .21	3.08 (0.62-15.41), *P* = .17
Asked doctor for another opioid prescription because I had lost/had stolen/someone else had used my prescription or medication	4 (3-5)	2 (1-4)	3 (2-5)	5 (3-9)	8 (5-11)	1.32 (0.58-3.02), *P* = .52	2.27 (0.91-5.68), *P* = .080	3.54 (1.65-7.62), *P* = .001
Given/sold my prescribed medication to someone else	1 (1-2)	1 (0-2)	1 (0-2)	2 (0-4)	1 (0-2)	1.03 (0.23-4.64), *P* = .97	1.96 (0.39-9.80), *P* = .41	1.10 (0.22-5.51), *P* = .91
Altered my dose in some other way when not advised to do so by a health professional	6 (5-8)	3 (2-6)	6 (4-8)	10 (7-15)	9 (7-12)	1.71 (0.87-3.33), *P* = .12	3.42 (1.68-6.99), *P* = .001	2.93 (1.52-5.66), *P* = .001
Taken my opioid medication by a different route than was prescribed	1 (1-2)	1 (0-2)	1 (1-2)	1 (0-4)	2 (1-4)	1.38 (0.25-7.59), *P* = .71	2.07 (0.29-14.89), *P* = .47	3.69 (0.76-17.90), *P* = .11
Used my opioid medication for other purposes (e.g., help sleep or to help with stress)	4 (3-5)	1 (0-2)	2 (1-4)	6 (4-11)	9 (7-12)	3.23 (0.90-11.52), *P* = .071	8.88 (2.50-31.54), *P* = .001	13.43 (4.08-44.19), *P* < .001
Report one or more non-adherent behaviors	38 (35-40)	20 (17-24)	38 (34-42)	45 (38-52)	53 (48-58)	2.41 (1.79-3.26), *P* < .001	3.22 (2.23-4.65), *P* < .001	4.43 (3.22-6.09), *P* < .001
Wave 2								
Asked doctor for an increase in prescribed dose	31 (28-33)	20 (16-24)	27 (23-32)	38 (31-46)	46 (40-52)	1.39 (0.98-1.98), *P* = .062	2.25 (1.45-3.50), *P* < .001	2.79 (1.93-4.05), *P* P < .001
Asked doctor for early prescription renewal because I had run out early	21 (18-23)	8 (6-12)	18 (15-22)	27 (20-35)	37 (51-66)	1.97 (1.18-3.29), *P* = .010	2.78 (1.50-5.13), *P* = .001	4.27 (2.53-7.20), *P* < .001
Used another person's opioid medication	4 (3-6)	2 (1-4)	2 (1-4)	10 (6-16)	8 (5-12)	0.95 (0.31-2.93), *P* = .93	4.87 (1.68-14.10), *P* = .004	3.73 (1.38-10.10), *P* = .010
Saved up my opioid medication	13 (11-15)	6 (4-8)	10 (8-14)	20 (14-27)	23 (18-28)	1.77 (1.00-3.13), *P* = .050	3.52 (1.86-6.67), *P* < .001	3.98 (2.27-6.99), *P* < .001
Gone to a different doctor to get more opioid medication and didn't tell my normal doctor	3 (2-4)	2 (1-4)	1 (1-3)	4 (2-10)	6 (3-9)	0.62 (0.18-2.12), *P* = .44	2.11 (0.63-7.04), *P* = .23	2.64 (0.96-7.28), *P* = .061

Table 4 (continued). *Non-adherent opioid use (past 3 months) at Wave 1 (n = 1,514) and Wave 2 (n = 1,201) according to group.*

Non-Adherent Opioid Medication Behavior (past 3 months)a	Total Sample (n = 1,514)	(A) Poor Physical Functioning Group n = 402	(B) Poor Coping and Physical Functioning Group n = 533	(C) Substance Use Problems Group n = 207	(D) Multiple Comorbid Problems Group n = 372	B vs A (ref) b	C vs A (ref) b	D vs A (ref) b
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	AOR (95% CI) *P* value	AOR (95% CI) *P* value	AOR (95% CI) *P* value
Asked doctor for another opioid prescription because I had lost/had stolen/someone else had used my prescription or medication	7 (6-9)	3 (2-6)	4 (2-6)	6 (3-12)	17 (13-22)	1.17 (0.51-2.65), *P* = .71	1.96 (0.77-4.99), *P* = .16	5.12 (2.48-10.56), *P* < .001
Given/sold my prescribed medication to someone else	2 (1-3)	3 (1-5)	1 (0-2)	3 (1-7)	3 (1-6)	0.38 (0.11-1.28), *P* = .12	1.09 (0.32-3.71), *P* = .89	1.11 (0.40-3.11), *P* = .84
Altered my dose in some other way when not advised to do so by a health professional	8 (7-10)	4 (2-6)	6 (4-8)	14 (9-21)	14 (11-19)	1.34 (0.65-2.76), *P* = .43	3.56 (1.66-7.63), *P* = .001	3.78 (1.91-7.51), *P* < .001
Taken my opioid medication by a different route than was prescribed	2 (2-3)	2 (1-4)	1 (1-3)	4 (2-9)	4 (2-7)	0.60 (0.19-1.87), *P* = .39	1.85 (0.57-6.04), *P* = .31	1.66 (0.58-4.73), *P* = .35
Used my opioid medication for other purposes (e.g., hel*P* slee*P* or to hel*P* with stress)	9 (8-11)	4 (2-6)	6 (4-9)	15 (10-21)	19 (14-24)	1.51 (0.74-3.12), *P* = .26	3.48 (1.61-7.52), *P* = .002	4.26 (2.15-8.44) *P* < .001
Report one or more non-adherent behaviors	44 (42-47)	28 (23-32)	40 (36-45)	56 (48-64)	66 (60-71)	1.37 (0.99-1.90), *P* = .059	2.59 (1.69-3.99) *P* < .001	3.32 (2.29-4.81) *P* < .001

a Wave 1: multivariate logistic regression results are presented here controlling for duration of continuous opioid medication as identified at wave 1, with the Poor Physical Functioning group as reference; Wave 2: multivariate logistic regression results are presented here controlling for duration of continuous opioid medication and non-adherent behavior as identified at wave 1, with the Poor Physical Functioning group as reference. An adjusted odds ratio (AOR) of 1 indicates the event is equally probable in each group, > 1 indicates the event is more likely to occur in the non-reference group relative to the reference group, and < 1 indicates the event is less likely to occur in the non-reference group, relative to the reference group. 95% CI: 95% confidence interval.

(OR = 1.84, 95%CI 1.41 – 2.41 *P* < .001) but not the latter (OR = 1.37, 95%CI 0.97 – 1.93, *P* = .072) group.

Wave 2 (Three Months)

A similar pattern of results was evident at 3 months after controlling for duration of continuous opioid use and the rate of each non-adherent behavior in wave 1 (Table 4). As at wave 1, all 3 risk groups had a greater number of people reporting one or more non-adherent behaviors than the Poor Physical Functioning group (Table 4). The rate of people reporting one or more non-adherent behaviors was significantly higher in the Multiple Comorbid Problems group than in the Poor Coping and Physical Functioning group (OR = 1.81, 95%CI 1.38 – 2.37, *P* < .001), with similar proportions to the Substance Use Problems group (OR = 1.32, 95%CI 0.93 – 1.86, *P* = .12). The latter 2 groups did not differ significantly (OR = 1.37, 95%CI 0.99 – 1.91, *P* = .060). The Poor Coping and Physical Functioning group had greater odds of only one non-adherent behavior (early script renewal) than the Poor Physical Functioning group. These 2 groups had greater odds of reporting requested dose increase, using diverted medication, stock-piling, unsanctioned dose alteration, and using medications for non-pain purposes compared to the Poor Physical Functioning group.

Discussion

Key Findings

We conducted a novel prospective investigation of whether putative risk factors for non-adherence (as described in prescribing guidelines and screening tools) predicted non-adherent opioid use by people with CNCP, while taking account of any interactions between these risk factors. We identified distinctive clusters of people with CNCP in the POINT cohort based on the risk factors identified by medical professionals and

researchers. These clusters show varying risks of non-adherence. We also found that the type and interplay between specific risk factors differentially predicted non-adherent opioid use.

The majority of the sample were grouped on the basis of their high likelihood of reporting poor physical functioning alone (Poor Physical Functioning group, 27%) or in combination with poor coping strategies and social support (Poor Coping and Physical Functioning group, 35%). The former group, in whom poor physical functioning was the only potential risk-factor for non-adherent behavior, were the most stable, with only 28% engaging in any non-adherent behavior at wave 2. The addition of poor coping and low social support were associated with 2-fold increase in the odds of reporting one or more non-adherent opioid medication-related behaviors. It is important to note that only two-fifths of people with CNCP had this interplay of functional, coping, and support risk factors for non-adherent opioid use. This suggests that the presence of these 3 risk factors does not guarantee non-adherent opioid use. This group comprises persons at moderate risk of non-adherent opioid use. It is important to note that the Poor Coping and Physical Functioning group were more likely to be male, unemployed, and report a low income relative to the Poor Physical Functioning group, suggesting relative socio-economic disadvantage.

The remaining two-fifths (34%) of the sample fell into 2 clusters: i) the Substance Use Problems group (14%), and ii) the Multiple Comorbid Problems group (25%). These participants reported greater socio-economic disadvantage (e.g., higher rates of unemployment) and greater health service use than the Poor Physical Functioning group. In these groups the increase in the number and type of potential risk factors was matched by increased rates of reported non-adherence compared to those who displayed only poor physical functioning. The 3 risk groups (Poor Coping and Physical Functioning group, Substance Use Problems group, and the Multiple Comorbid Problems group) had greater odds of requesting increased doses, early script renewals, and stock-piling at both time points than the Poor Physical Functioning group, even after controlling for time using opioids. However, those patients with CNCP who fell into those groups with substance use problems and mental health problems were also more likely to report requesting an increased dose and non-pain related opioid use. The Multiple Comorbid Problems group reported higher rates of doctor-shopping and more frequent loss of scripts than those reporting only poor physical functioning. Again, it is important to note that not all participants falling into this cluster reported non-adherent opioid use. Clearly, patients with such combinations of risk factors should not be denied access to opioids for their pain – but the reports of non-adherent opioid use by three-fifths of this group indicate the necessity to implement strategies to monitor and reduce risk in these higher risk patients.

Interpretation

Overall, this study suggests 3 important conclusions: i) not all people who report potential risk factors for non-adherence display non-adherent opioid use, ii) the type of potential risk factor and complexity of risk presentation is important when establishing a treatment plan and deciding if the benefits of opioids will outweigh risks and if additional monitoring and review are required, and iii) there are differential associations between risk factor clusters and types of non-adherent behaviors (i.e., people with a given risk factor do not necessarily have a high likelihood of engaging in all non-adherent behaviors). Consistency in the pattern of group differences at wave 1 and wave 2 in rates of non-adherent opioid use lends weight to the reliability of these outcomes. Screening tools often equally weight risk factors in scoring, with cut-off scores adopted to indicate potential risk for non-adherence. Such an approach does not take into account the relative predictive value of each factor independently and when in the presence of other specific factors. These measures are often recommended and implemented in clinical practice as they are brief, easy to administer, and relatively inexpensive (15). However, these findings reinforce the need for clinical judgement and inquiry when adopting these measures, and support a multi-faceted approach to assessment, using clinical interviews in combination with self-report screening measures where possible given evidence of greater predictive validity (15,50).

Generalisability and Limitations

The sample may not be representative of all people who are prescribed opioids for CNCP. However, additional data from a random sample of recruiting pharmacies for the study (n = 71) showed striking similarity between the characteristics of customers purchasing opioids during the 6 week recruitment window in those pharmacies compared to the POINT sample: 52% were female (the POINT cohort was 55% female); and 7% were 18 – 34 years, 55% 35 – 64 years, and 38% 65+ years (vs. 5%, 62%, and 33%, respectively, in the POINT

cohort). Of these customers, 63% were prescribed oxycodone, 17% morphine, and 21% fentanyl patches (vs. 62%, 15%, and 21%, respectively, in the POINT cohort) (56).

The risk factors we studied represented the main risk factors in the literature that were also measureable with data available from the POINT cohort. These variables were representative of those commonly considered when assessing risk for non-adherent opioid use (often via self-report), and hence this paper makes a useful contribution to the evidence base on factors that need to be considered in deciding whether or not to prescribe opioids. It is important to note that the POINT sample was not selected on the basis of non-adherent patterns of medication-related behaviors. Indeed, rates of using diverted medications and tampering with prescribed medications were low (≤ 2% of total sample). However, approximately two-fifths reported at least one non-adherent opioid medication-related behavior in the 3 months prior to baseline. This means that it cannot be assumed that risk factors reported at wave 1 occurred prior to non-adherent behavior. Furthermore, there are potential biases in self-report, although self-report is generally reliable when there are no disincentives for being honest (57), and participants have been assured of anonymity and confidentiality (as was the case in the study). The period for prospective analysis was brief (3 months) although results were replicated over both time points. Extension of the period of observation will provide clarity for the enduring nature of these patterns of behaviors.

Conclusions

Overall, these results suggest that risk factors described in prescribing guidelines and screening tools should not be equally weighted in the decision to prescribe because they differentially predict non-adherent opioid use. Instead, the type and interplay between risk factors must be important considerations, with particular emphasis on substance use and mental health problems. It is important to acknowledge that not all people who report potential risk factors display non-adherent opioid use. These findings emphasize the need for strategies to monitor and reduce risk for those patients displaying particular clusters of multiple risks.

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Author Contributions

LD, BL, GC, SN, WH, RPM, and RB contributed to the development of the study for the purposes of the funding proposal and development of the study design. AP, LD, and RB led writing for the first draft. All authors contributed to the critical review of the manuscript. All authors read and approved the final manuscript.

Conflict of interest

BL, LD, and RPM have received untied educational grants from Reckitt Benckiser for the post-marketing surveillance of opioid substitution therapy medications in Australia and the development of an opioid-related behavior scale. SN has been an investigator on untied educational grants from Reckitt Benckiser. LD, BL, and RB have received untied educational grants from Mundipharma to conduct surveillance of the use of pharmaceutical opioids in Australia. All such studies' design, conduct, and interpretation of findings are the work of the investigators; the funders had no role in those studies.

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