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Research paper

Methods and predictors of tampering with a tamper-resistant controlled-release oxycodone formulation

Amy Peacock [a,*], Louisa Degenhardt [b], Antonia Hordern [b], Briony Larance [b], Elena Cama [b], Nancy White [c,d], Ivana Kihas [b], Raimondo Bruno [a]

[a] School of Medicine, University of Tasmania, Hobart, Tasmania, Australia
[b] National Drug and Alcohol Research Centre, University of New South Wales, NSW, Australia
[c] Sydney Medical School, Sydney University, NSW, Australia
[d] University of Adelaide, South Australia, Australia

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ABSTRACT

Background: In April 2014, a tamper-resistant controlled-release oxycodone formulation was introduced into the Australian market. This study aimed to identify the level and methods of tampering with reformulated oxycodone, demographic and clinical characteristics of those who reported tampering with reformulated oxycodone, and perceived attractiveness of original and reformulated oxycodone for misuse (via tampering).

Methods: A prospective cohort of 522 people who regularly tampered with pharmaceutical opioids and had tampered with the original oxycodone product in their lifetime completed two interviews before (January–March 2014: Wave 1) and after (May–August 2014: Wave 2) introduction of reformulated oxycodone.

Results: Four-fifths (81%) had tampered with the original oxycodone formulation in the month prior to Wave 1; use and attempted tampering with reformulated oxycodone amongst the sample was comparatively low at Wave 2 (29% and 19%, respectively). Reformulated oxycodone was primarily swallowed (15%), with low levels of recent successful injection (6%), chewing (2%), drinking/dissolving (1%), and smoking (<1%). Participants who tampered with original and reformulated oxycodone were socio-demographically and clinically similar to those who had only tampered with the original formulation, except the former were more likely to report prescribed oxycodone use and stealing pharmaceutical opioid, and less likely to report moderate/severe anxiety. There was significant diversity in the methods for tampering, with attempts predominantly prompted by self-experimentation (rather than informed by word-of-mouth or the internet). Participants rated reformulated oxycodone as more difficult to prepare and inject and less pleasant to use compared to the original formulation.

Conclusion: Current findings suggest that the introduction of the tamper-resistant product has been successful at reducing, although not necessarily eliminating, tampering with the controlled-release oxycodone formulation, with lower attractiveness for misuse. Appropriate, effective treatment options must be available with increasing availability of abuse-deterrent products, given the reduction of oxycodone tampering and use amongst a group with high rates of pharmaceutical opioid dependence.

Introduction

Although opioid medications play an important role in pain management, their use outside the bounds of a doctor's prescription (which we term here "extra-medical use"; Larance, Degenhardt, Lintzeris, Winstock, & Mattick, 2011) has been cause for concern because of the risk of serious adverse events including opioid overdose (Dhalla et al., 2009; Paulozzi, Budnitz, & Xi, 2006). Pharmaceutical opioids now comprise the majority of fatal and non-fatal drug overdoses in the US (Compton & Volkow, 2006; Paulozzi et al., 2006) and more recently in countries like Australia (Roxburgh, Burns, Hall, & Degenhardt, 2014).Opioids differ in the extent to which they are likely to be associated with hazardous patterns of use, due to different potencies, pharmacokinetic characteristics and propensities for dependence (differing 'abuse

* Corresponding author at: School of Medicine (Psychology), University of Tasmania, Private Bag 30, Hobart, Tasmania 7001, Australia. Tel.: +61 3 6226 7458; fax: +61 3 62262 883.
E-mail address: Amy.Peacock@utas.edu.au (A. Peacock).

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liability') (Grudzinskas et al., 2006; Quinn, Wodak, & Day, 1997; Schuster, 2006; Trescot, Datta, Lee, & Hansen, 2008). The past decade has seen pharmaceutical companies make significant investment in the development of formulations that are less prone to tampering (particularly via injection), dependence and diversion (Katz et al., 2011; Romach, Schoedel, & Sellers, 2013; US Department of Health and Human Services, Food and Drug Administration, & (CDER), C. f. D. E. a. R., 2013). The Food and Drug Administration in the US has developed labelling guidelines for 'abuse deterrent' formulations of pharmaceutical opioids, one form of which can involve tamper-resistant formulations (US Department of Health and Human Services et al., 2013).

In April 2014, a new formulation of oxycodone was introduced with public subsidy in Australia which was intended to have these tamper-resistant properties. This formulation of oxycodone is a controlled-release tablet, but its physicochemical properties make the tablets more difficult to tamper with and/or crush into a fine powder (Cone, Giordano, & Weingarten, 2013). Reformulated oxycodone is more resilient to chemical extraction and does not demonstrate an accelerated dissolution when placed in ethanol. The formulation comprises a polymer; a curing process takes place during manufacture whereby the controlled-release tablet is heated above the melting point of the polymer, which produces a hard plastic-like effect to the tablet upon cooling. If crushed, it produces large pieces (rather than fine powder), which turn into a glutinous gel-like mixture when combined with water, rendering the mixture difficult to use via intranasal or intravenous routes of administration (ROA; Sellers, Perrino, Colucci, & Harris, 2013). US studies suggest that reformulated oxycodone may be less attractive for misuse via tampering (Sellers et al., 2013), and much lower levels of diversion and use have been observed (Butler et al., 2013; Cassidy, DasMahapatra, Black, Wieman, & Butler, 2014; Severtson et al., 2013).

In Australia, the first national post-marketing surveillance study of the controlled-release oxycodone reformulation, called the National Opioid Medication Abuse Deterrence (NOMAD) study, is underway. Using data from a prospective cohort forming part of the NOMAD study, the aims of this paper are to:

(1) Examine the levels of tampering with the controlled-release oxycodone reformulation among people who regularly tamper with pharmaceutical opioids;
(2) Examine predictors of tampering with the controlled-release oxycodone reformulation in the cohort;
(3) Describe the methods of tampering attempts with the controlled-release oxycodone reformulation; and
(4) Identify potential differences in perceived attractiveness for misuse (via tampering) between the original and reformulated controlled-release oxycodone product (amongst those who tampered with both forms).

Methods

Participants and procedure

The complete methods of the broader NOMAD study and the cohort component are available elsewhere (Degenhardt et al., 2015; Larance et al., 2015; Peacock et al., 2015). Participants (n = 606) were recruited through a variety of settings and services in Sydney, New South Wales (NSW), Adelaide, South Australia (SA) and Hobart and Launceston, Tasmania (TAS) including Needle–Syringe Programs (NSPs), snowballing and word-of-mouth, opioid substitution therapy (OST) clinics/prescribers, community pharmacies, and advertisements in newspapers and street media and other health/outreach services.

Individuals were eligible to participate in the cohort if they were English language proficient, over 18 years of age, reported extra-medical pharmaceutical opioid use on a monthly or more frequent basis in the last six months, and reported injecting, snorting, chewing, smoking and/or dissolving and drinking a pharmaceutical opioid in the last month and on a monthly or more frequent basis in the past six months. Participants were excluded if they had not been a resident of the city/state for the six months prior to the interview, had been in prison for the past month, had only tampered with an OST medication, or if they reported only using their opioid medication as per a doctor's instructions. Participants completed two waves of structured computer-assisted interviews (Wave 1 January–March 2014 prior to the release of the reformulated oxycodone, and Wave 2 May–August 2014 following its release) and reimbursed $50AUD and $40AUD on the two occasions for time and out-of-pocket expenses.

Ethics

This study has approval from the Ethics Review Committee (Royal Prince Alfred Hospital Zone) of the Sydney Local Health District, AIDS Council of New South Wales, Tasmanian Health and Medical Human Research Ethics Committee, University of Adelaide Human Research Ethics Committee and Southern Adelaide Clinical Human Research Ethics Committee. Access and site approvals were obtained from the following local area health ethics committees governing clinic sites: Sydney Local Health District, South Eastern Sydney Local Health District, South Western Sydney Local Health District and Western Sydney Local Health District.

Key measures

Patterns of original and reformulated oxycodone use

Lifetime and past month prescribed and non-prescribed use of OxyContin® original (Wave 1 and 2 interviews) and reformulated (Wave 2 interview only) 10–80 mg tablets were assessed. Methods of tampering and ROA (including injection, snorting, chewing, smoking and dissolving/drinking) were also assessed. Medication prompt cards with photographs of opioid medications and tablet sizes were used to ensure correct identification of target drugs and formulation.

Wave 1 correlates of tampering with reformulated oxycodone (Wave 2)

Variables were selected based on previous research showing demographic (e.g., age, prison history), physical and mental health (e.g., history of trauma), and drug use history correlates of injecting drug use (e.g., Kerr et al., 2009; Strathdee et al., 2008) and non-medical use of pharmaceutical opioid use (e.g., Becker, Sullivan, Tetrault, Desai, & Fiellin, 2008). During the Wave 1 interview participants were asked a range of demographic questions. The chronic conditions section of the Composite International Diagnostic Interview (CIDI; Kessler & Üstün, 2004) was included to assess problematic physical conditions in the past 12 months. The Patient Health Questionnaire (PHQ-9) and the Generalised Anxiety Disorder (GAD-7) modules of the Patient Health Questionnaire (Kroenke, Spitzer, Williams, & Lowe, 2010) were included; symptoms indicating moderate to severe depression were defined as a PHQ-9 score $\geq$10 (Kroenke, Spitzer, & Williams, 2001), symptoms of moderate to severe anxiety were defined as a GAD-7 score $\geq$10 (Spitzer, Kroenke, Williams, & Löwe, 2006). The Primary Care PTSD screen (PC-PTSD) was used to measure post-traumatic stress disorder (PTSD), with a score greater than 3 indicating presence of PTSD (Prins et al., 2004).

Participants reported their past month use (prescribed and not prescribed) of all available forms of morphine, methadone,

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buprenorphine, fentanyl, prescription and over-the-counter codeine, and tramadol, as well as past six month use of heroin, methamphetamine, cocaine, and alcohol. The CIDI (World Health Organisation, 2001) was administered to assess past 12 month pharmaceutical opioid dependence based on International Classification of Diseases (ICD-10) criteria. The Severity of Dependence Scale (SDS) was used to assess dependence on heroin (indicated by a score ≥5; Gossop et al., 1995) and methamphetamine (indicated by a score ≥4; Topp & Mattick, 1997). The 3-item Alcohol Use Disorders Identification Test (AUDIT-C) was included to assess alcohol-related problems (indicated by a score ≥5; Babor, Higgins-Biddle, Saunders, & Monteiro, 2001). The Wave 1 interview also included questions regarding past six month source(s) of all pharmaceutical opioids.

Methods of tampering with the reformulated oxycodone product

A module was included in the Wave 2 interview to assess methods for tampering with reformulated oxycodone. The module asked participants to provide detailed information about methods used to prepare reformulated oxycodone, including cleaning the tablet, chopping and grinding, tablet dissolution and heating. Details regarding methods of preparation were asked as an open-question and then coded by the trained interviewer to avoid bias in reporting. Participants were also asked the length of time each process took, where they learnt about each method, the ROA they used, and whether each method was perceived as successful.

Attractiveness of original and reformulated oxycodone for tampering

An adapted 7-item version of the Opioid Attractiveness Scale (Butler et al., 2010a, 2010b) was administered to assess attractiveness of original and reformulated oxycodone for injection. Items comprised statements regarding willingness to tamper in future (i.e., 'would definitely tamper with it again'), pleasure associated with use (i.e., 'is unpleasant to use'), difficulty and pain associated with injecting (i.e., 'difficult to inject' 'painful to inject'), difficulty with preparation (i.e., 'easy to cut up' 'easy to dissolve'), and perceived harms of tampering (i.e., 'contains fillers that cause safety issues when injecting'). Responses were rated on a 5-point scale (0 'Strongly disagree' to 4 'Strongly agree'); binary variables were created to identify those who agreed or strongly agreed with each statement compared with neutral and disagreement responses.

Data analysis

SPSS Statistics Version 21 (IBM, Somers, NY) was used to calculate descriptive statistics: percentage and 95% confidence interval (95% CI) for categorical outcomes and mean and standard deviation (M, SD) for continuous outcomes. Odds ratios (OR) with 95% CI are reported for: (i) between-subject correlates of reporting tampering with reformulated oxycodone, and (ii) within-subject differences in attractiveness ratings for original and reformulated oxycodone from Wave 1 to Wave 2; the latter were calculated taking into account correlation between observations. Across all analyses, significance levels were maintained at $p < 0.050$.

Results

Sample characteristics and use of the original oxycodone prior to reformulation oxycodone introduction

A total of 1321 people expressed interest in the study, and of these, the research team made contact with 1176. Of the 692 people who were screened and found eligible to participate, 606 completed the Wave 1 interview (NSW: $n = 303$; SA: $n = 150$; TAS: $n = 153$) and 547 completed the Wave 2 interview (91% retention rate; NSW: $n = 269$; SA: $n = 140$; TAS: $n = 138$). The socio-demographic characteristics of those who completed only the Wave 1 interview and those who had just completed both Wave 1 and Wave 2 interviews were compared, and differences were largely insignificant. The exception to this was that participants who completed both interviews had decreased odds of having left school before year 10 compared to those participants who only completed the Wave 1 interview (OR 0.56, 95% CI: 0.32–0.97, $p < 0.05$). This paper comprises data collected at Wave 1 and 2 interviews, with the sample restricted to those who completed both interviews and reported ever tampering with the oxycodone product ($n = 522$). Participants included in the final analytic sample were demographically similar to those who were excluded ($n = 85$), with the exception that those who had completed with both interviews had lower odds of reporting being homeless at baseline compared to those who only completed Wave 1 interviews (OR 0.48, 0.28–0.82, $p < 0.01$).

The samples ($n = 522$) were predominantly male (69%) with a mean age of 41 years (SD = 9.3, range 34–47). Participants typically reported being unemployed (82%), having a prison history (63%), and receiving a low income (59%) comparable with Australian unemployment and disability benefits (less than AUD$400 per week). Nearly one-third (29%) had not completed year 10 schooling, and almost one-fifth (16%) were homeless. Two-thirds (71%) had been prescribed an opioid medication in the preceding month, half (49%) had received OST within this period, and four-fifths (81%) had tampered with the original formulation in the month prior to Wave 1.

Use of original and reformulated oxycodone post-introduction

Four-fifths (82%) of the NOMAD cohort were aware of the change in formulation; one in three (29%) reported ever using reformulated oxycodone at Wave 2 (Table 1). One-fifth (18%) had ever attempted to tamper with reformulated oxycodone; only one-tenth (12%) reported a "successful" tampering attempt, with 8% reportedly successfully tampering with reformulated oxycodone in the past month, and only one-third (33%) of these participants doing so on more than one day in the past month. The primary ROA adopted for any reportedly 'successful' use of tampered reformulated oxycodone was swallowing (15%), followed by injecting (9%), chewing (2%), and dissolving and drinking (2%). Very few participants reported smoking as a ROA, with no reports of snorting. In contrast, one-quarter (25%) of the sample had injected the original formulation in the month prior to Wave 2; extent of chewing, dissolving and drinking, smoking and snorting original oxycodone were similarly low.

Wave 1 predictors of tampering with reformulated oxycodone

Comparisons were run between those who reported ever tampering with reformulated oxycodone prior to Wave 2 ('*Reformulated Tampering group*'; $n = 61$) versus those who reported only ever tampering with original formulation prior to Wave 1 ('*Original Tampering group*'; $n = 460$).

The groups were broadly similar in regard to socio-demographic profile, prescription history, mental and physical health, past month use of pharmaceutical and other drugs, and sources of prescription medication at Wave 1 (Table 2). There were some exceptions: the '*Reformulated Tampering group*' reported sevenfold increased odds of past month prescribed use of the original oxycodone product at Wave 1 compared to the '*Original Tampering group*' (33% versus 7%, respectively). Compared to the '*Original Tampering group*', the '*Reformulated Tampering group*' had fourfold increased odds of stealing pharmaceutical opioids from a stranger or store (4% versus 15%), and twofold increased odds of

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Table 1
Tampering with original and reformulated oxycodone among the NOMAD cohort at Wave 2 ($n = 522$).

	Total sample ($n = 522$)	
	% (95% CI)	*n*
Reformulated product		
Aware of reformulation~	82 (78–85)	369
Ever used reformulation	29 (25–33)	150
Past month reformulation use	19 (16–22)	98
Ever tried tampering with reformulation	18 (15–21)	91
Ever successfully tampered with reformulation	12 (9–15)	61
Past month tampering with reformulation	8 (6–10)	39
Of those who tried to tamper in the last month		
Tampering with reformulation for >1 day	33 (21–49)	13
Reformulation routes of administration		
Swallowed past month	15 (12–19)	79
Injecting		
Ever tried	15 (12–18)	76
Ever successfully injected	9 (7–12)	47
Successfully injected past month	6 (4–8)	30
Snorting		
Ever tried	0 (0–1)	0
Ever successfully snorted	0 (0–1)	0
Successfully snorted past month	0 (0–1)	0
Smoking		
Ever tried	1 (0–2)	3
Ever successfully smoked	1 (0–2)	3
Successfully smoked past month	0 (0–1)	1
Chewed		
Ever tried	4 (2–5)	18
Ever successfully chewed	2 (1–4)	12
Successfully chewed past month	2 (1–4)	12
Dissolve/drank		
Ever tried	3 (2–4)	13
Ever successfully dissolved/drank	2 (1–4)	10
Successfully dissolved/drank past month	1 (0–2)	5
Original formulation (past month)		
Used	25 (22–29)	131
Successfully injected	25 (22–29)	131
Successfully snorted	0 (0–1)	1
Successfully smoked	1 (0–2)	3
Successfully chewed	0 (0–1)	2
Successfully dissolved/drank	0 (0–1)	1

Note: The sample size was 469 for this item as it was added to the interview one fortnight into data collection.

experiencing past month non-everyday pain (46% versus 61%) and past month cocaine use (19% versus 31%). Compared to the '*Original Tampering group*', the '*Reformulated Tampering group*' also had lower odds of reporting past month prescribed OST medication use (51% versus 32%) and moderate/severe anxiety (45% versus 27%). Past month prescribed OST use at Wave 1 remained a significant predictor of not reporting tampering with the reformulated product at Wave 2 when included in a multivariate model with demographic variables and Wave 2 frequency of injection (OR = 0.47, 95% CI 0.26–0.85). However, this association was not statistically significant when those variables which were significant at the univariate level were included in the model (OR = 0.57, 95% CI 0.30–1.10). In the multivariate model, significant predictors of reformulation tampering comprised prescribed use of the original oxycodone (OR = 4.31, 95%CI 2.12–8.76), stealing pharmaceutical opioids from a stranger or store (OR = 5.09, 95% CI 1.82–14.22), and the absence of moderate/severe anxiety (OR = 0.45. 95% CI 0.23–0.88); no other variables in the model were significant.

The '*Reformulated Tampering group*' and the '*Original Tampering group*' were similar in regard to rates of drug-related problematic behaviours and harms at Wave 2, including needle- and equipment-sharing, injection-related injuries and diseases (IRID), accidental overdose, and hospital admissions for any health-related reason (Table 2) even after controlling for frequency of injection.

ROA and methods of tampering with reformulated oxycodone

Nearly one-fifth (16%, $n = 86$) of the NOMAD cohort completed a detailed module in Wave 2 regarding attempts to tamper with reformulated oxycodone. Of these participants, four-fifths (79%, $n = 68$) had attempted to inject, one-fifth (17%, $n = 15$) had tried to chew, and over one-tenth (14%, $n = 12$) had tried to dissolve/drink reformulated oxycodone.

Preparation of pharmaceutical opioid tablets for injection typically involves four stages completed in varying order: cleaning the tablet, breaking up the tablet, dissolving the tablet, and heating the tablet (Patel et al., 2012); the following refers to participants reported procedure for preparation for successful and unsuccessful tampering attempts. The majority of participants (68%) self-reported that they did not clean reformulated oxycodone during a preparation attempt; over one-third (37%) reported wiping, swabbing, and/or rinsing the tablet (26%: unspecified liquid, 11%: specified liquid, typically water or alcohol) (Table 3). One-third of participants (30%) did not break up the tablet during a preparation attempt; over two-thirds (68%) reported cutting up/crushing reformulated oxycodone; only one-tenth of participants (10%) reported scraping, grinding, grating and/or filing the tablet. Similarly, one-third (29%) did not use any substance to break down the tablet during a preparation attempt; instead, the majority of participants (65%) used water to attempt to dissolve reformulated oxycodone. One-quarter of the participants (27%) did not use heat during the preparation process; two-fifths (41%) had attempted to heat reformulated oxycodone in a spoon; and one-quarter (28%) had used an oven, microwave and/or stove.

Three-quarters (87%, $n = 75$) of participants reported using one preparation method (successful or unsuccessful) to tamper, one-tenth (12%, $n = 10$) reported using two preparation methods, and one person reported using three preparation methods (total of 98 methods; note that preparation methods may not be distinct in regard to the order of preparation stages and activities completed at each preparation stages). Participants reported preparation time for 79 methods, with a median time of 15 min (although there was considerable variability in the duration of preparation; minimum and maximum time of 1 min and 24 h, respectively). Source of information regarding tampering method was reported for 87 methods. Three-fifths (59%, $n = 51$) of the methods were self-guided experimentation, one-quarter (24%, $n = 21$) were attempted based on information from friends, and 15% ($n = 13$) were adopted based on information from internet sources.

Attractiveness of original and reformulated oxycodone for misuse via tampering

Within-subject analyses of attractiveness items were restricted to those participants who had tampered with the original formulation one month prior to Wave 1, and with original and reformulated oxycodone one month prior to Wave 2 ($n = 19$; Table 4). Ratings of willingness to tamper, difficulty and pain of injection, harms, and difficulty of preparation (cutting up and dissolving) for the original formulation did not significantly differ at Wave 1 and Wave 2. In contrast, participants reported sixfold increased odds of rating reformulated oxycodone painful to inject compared to the original formulation at Wave 2 (40% versus 11%, respectively). Compared to original oxycodone, fewer people rated reformulated oxycodone as easy to cut-up (79% versus 21%) and dissolve (74% versus 14%) compared to original oxycodone. While less than 5% of participants reported the original formulation as unpleasant to tamper with and difficult to inject at Wave 2, nearly half the participants (50% and 47% respectively) perceived reformulated oxycodone in this way.

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Table 2
Predictors of tampering with reformulated oxycodone among the NOMAD cohort at Wave 2 ($n = 522$).

Characteristics[a]	A. Original tampering group (no tampering with reformulation) $n = 460$% (95% CI)	B. Reformulated tampering group (also tampered with original formulation) $n = 61$% (95% CI)	A (ref) versus B[b] OR (95% CI)
Wave 1			
Demographics			
Mean age (SD)	41 (9.5)	39 (7.9)	t (85) = 1.16
Male	69 (65–73)	69 (56–79)	0.98 (0.55–1.78)
Unemployed	82 (78–85)	84 (72–91)	1.11 (0.54–2.27)
Education <year 10	29 (25–34)	21 (13–33)	0.65 (0.34–1.24)
Income <$400 per week	59 (54–63)	56 (43–68)	0.88 (0.51–1.50)
Homeless/no fixed abode	15 (12–19)	20 (12–31)	1.34 (0.68–2.65)
Been to prison	64 (59–68)	57 (45–68)	0.77 (0.45–1.32)
Opioid prescription history (past month)			
Prescribed pharmaceutical opioid	71 (67–75)	67 (55–78)	0.83 (0.47–1.48)
Prescribed original sustained-release oxycodone formulation (10–80 mg)	7 (5–9)	33 (22–45)	**6.75 (3.54–12.89)**[***]
Received OST	51 (47–56)	32 (21–44)	**0.44 (0.25–0.79)**[**]
Physical health			
Non-everyday pain (past month)	46 (41–50)	61 (48–72)	**1.87 (1.07–3.25)**[*]
Problematic physical condition (12 months)	73 (69–77)	85 (74–92)	2.01 (0.96–4.22)
Mental health			
Moderate/severe depression	62 (57–66)	61 (48–73)	0.99 (0.56–1.75)
Moderate/severe anxiety	45 (41–50)	27 (17–40)	**0.44 (0.24–0.83)**[**]
PTSD	43 (38–47)	41 (29–55)	0.95 (0.54–1.70)
Prescription and non-prescription opioid medications used (past month)			
Used morphine	64 (59–68)	71 (58–80)	1.35 (0.75–2.42)
Used methadone syrup	50 (46–55)	45 (33–58)	0.80 (0.47–1.38)
Used Physeptone	13 (11–17)	17 (9–28)	1.30 (0.62–2.69)
Used buprenorphine/buprenorphine-naloxone	30 (26–34)	28 (19–41)	0.93 (0.51–1.69)
Used fentanyl	7 (5–10)	13 (7–24)	2.04 (0.89–4.66)
Used prescription/OTC codeine	62 (57–66)	58 (46–70)	0.87 (0.51–1.51)
Used tramadol	14 (11–18)	10 (5–20)	0.67 (0.28–1.61)
ICD-10 pharmaceutical opioid dependence (past 12 months)	52 (47–56)	50 (32–62)	0.93 (0.54–1.60)
Other drug use			
Used heroin (past 6 months)	64 (59–68)	71 (58–80)	1.36 (0.76–2.44)
Heroin dependence (SDS score ≥5)	40 (36–45)	38 (26–51)	0.90 (0.51–1.59)
Used methamphetamine (past 6 months)	73 (68–77)	79 (67–87)	1.39 (0.73–2.66)
Methamphetamine dependence (SDS score ≥4)	25 (21–29)	26 (16–38)	1.06 (0.57–1.98)
Used cocaine (past 6 months)	19 (16–23)	31 (21–44)	**1.94 (1.08–3.50)**[*]
Used alcohol (past 6 months)	72 (68–76)	66 (53–76)	0.74 (0.42–1.31)
Risky drinker (AUDIT-C score ≥3)	37 (33–42)	33 (23–46)	0.84 (0.47–1.48)
Used cannabis (past 6 months)	79 (75–82)	85 (74–92)	1.54 (0.74–3.24)
Source of pharmaceutical opioids (past 6 months)			
Prescription from a doctor for actual pain/medical reason	65 (60–69)	66 (53–77)	1.06 (0.60–1.89)
Prescription from a doctor for no medical reason	14 (11–18)	12 (6–22)	0.81 (0.35–1.85)
Prescription from multiple doctors	12 (9–15)	18 (11–30)	1.70 (0.83–3.48)
Prescription from a doctor who prescribes dishonestly	7 (5–10)	12 (6–23)	1.78 (0.75–4.23)
Forged prescription	3 (2–5)	5 (2–14)	1.54 (0.43–5.49)
Bought from a dealer	81 (77–84)	90 (80–95)	2.14 (0.89–5.13)
Bought on the internet	3 (2–5)	2 (0–9)	0.58 (0.08–4.52)
Bought from a patient who sells their medications	72 (68–76)	83 (72–91)	1.94 (0.96–3.95)
Stolen from work (hospital, nursing home, clinic etc.)	1 (1–3)	5 (2–14)	3.97 (0.97–16.29)
Stolen from stranger, store or other place	4 (3–6)	15 (8–26)	**4.08 (1.75–9.49)**[**]
Shared by someone	68 (64–72)	72 (59–82)	1.18 (0.65–2.15)
Wave 2			
Drug use risk and harms (past month)			
Used a needle after someone else	5 (3–7)	2 (0–9)	0.33 (0.04–2.50)
Used other injecting equipment after someone else	15 (12–19)	21 (13–33)	1.51 (0.78–2.93)
Re-used own needle	43 (38–47)	53 (40–65)	1.46 (0.86–2.50)
Non-serious IRID	24 (20–28)	25 (17–38)	1.03 (0.55–1.91)
Potentially serious IRID	11 (9–14)	16 (9–28)	1.58 (0.75–3.29)
Serious IRID	1 (1–3)	3 (1–11)	2.57 (0.51–3.00)
Accidental overdose	3 (2–5)	5 (2–14)	1.65 (0.46–5.91)
Admitted to hospital (any health-related reason)	11 (9–14)	15 (8–26)	1.38 (0.64–2.97)

[a] The sample is restricted to those participants who had ever tampered with the original formulation prior to Wave 1 and did not report ever tampering with the reformulated oxycodone ('*Original Tampering group*') and those who had ever tampered with the original reformulation prior to Wave 1 and reformulated oxycodone prior to Wave 2 ('*Reformulated Tampering group*'). The percentage of participants who received opioid substitution therapy (OST) refers to any prescription of methadone, Biodone, Subutex, Suboxone film and/or Suboxone tablets in the last 28 days. Physical conditions were defined as past-12 month problematic experience of arthritis, back/neck pain, chest pain, frequent/severe headaches, visceral pain, hepatitis C, asthma, stroke, heart attack, sleep apnea, chronic obstructive pulmonary disease, diabetes, cancer, and/or pelvic pain. Moderate/severe depression and anxiety was determined based on a score ≥10 on the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) and/or the Generalised Anxiety Disorder-7 Modules of the Patient Health Questionnaire (GAD) (Spitzer et al., 2006), respectively. International Classification of Diseases (ICD-10) pharmaceutical opioid dependence was assessed using the Composite Diagnostic Interview. Heroin and methamphetamine dependence were assessed using the Severity of Dependence Scale (SDS). Risky alcohol consumption was assessed using the Alcohol Use Disorders Identification Test short form (AUDIT-C) (Babor et al., 2001). *Non-serious IRID* includes: transient redness, transient swelling, hives, 'dirty hit', hitting an artery, numbness or pins and needles and collapsed/blocked veins; *potentially serious IRID* includes: abscesses, cellulitis, thrombophlebitis, oedema, puffy hands syndrome, and injecting sinus; *serious IRID* includes: systemic infections, deep vein thrombosis, gangrene, amputation and venous ulcer.

[b] Odds ratios (OR) are presented here with 95% confidence intervals (95% CI); an odds ratio of 1 indicates the event is equally probable at each time point, >1 indicates the item was endorsed by more people in the '*Reformulated Tampering group*' compared to the '*Original Tampering group*', and <1 indicates the item was endorsed by fewer people in the '*Reformulated Tampering group*' compared to the '*Original Tampering group*'. OTC: over-the counter; SD: standard deviation.

[*] $p < 0.050$.
[**] $p < 0.010$.
[***] $p < 0.001$.

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Table 3
Techniques used in attempts (successful and unsuccessful) to tamper with reformulated oxycodone ($n = 86$).

Method	Participants who completed reformulation tamper module ($n = 86$)	
	% (95% CI)	*n*
Clean tablet[a]		
Did not clean	68 (57–77)	57
Wipe/swab/rinse (unspecified liquid)	26 (18–37)	22
Wipe/swab/remove (specified liquid)	11 (6–19)	9
Tablet breakup[b]		
Did not break up	30 (21–41)	25
Crushing/cutting	68 (57–77)	56
Scraping/grinding/grating/filing	10 (5–18)	8
Dissolve tablet[c]		
Did not dissolve	29 (20–40)	23
Water	65 (54–75)	52
Acetone	5 (2–12)	4
Other liquid (specified and unspecified)	10 (5–19)	8
Heat tablet[b]		
Did not heat	27 (18–37)	22
Oven/microwave/stove	28 (19–38)	23
Heat in spoon	41 (31–52)	34
Other heat	15 (9–24)	12

Note: Tampering was defined as attempting to inject, smoke, snort, chew, and/or drink/dissolve reformulated oxycodone (designed for oral administration), although no participants reported snorting reformulated oxycodone.

[a] Two participants had missing data for this item; specified liquids predominantly comprised alcohol and water; other heat typically comprised heating with a cigarette lighter.

[b] Three participants had missing data for this item.

[c] Six participants had missing data for this item; specified liquids typically comprised alcohol and vinegar.

Discussion

This study aimed to assess levels of use and methods of tampering with a tamper-resistant formulation of controlled extended-release oxycodone among a cohort of people who regularly tamper with pharmaceutical opioids. Low levels of use and tampering with reformulated oxycodone were evident, with only one-tenth (12%) ever successfully tampering with reformulated oxycodone despite one-fifth (18%) attempting to tamper with reformulated oxycodone, and the majority (88%) of the sample reporting recently tampering with the original oxycodone formulation prior to introduction. Furthermore, the majority (66%) of people who had tampered with reformulated oxycodone reported use only once in the preceding month, suggesting low levels of pervasive use. Most notably, the primary ROA for reformulated oxycodone reported by this cohort of people who regularly tamper with pharmaceutical opioids was swallowing (15%), with few (6%) reporting recent successful injection, and even fewer reporting successfully chewing, smoking, and drinking/dissolving reformulated oxycodone. These findings contrast with US research (Butler et al., 2013) which showed higher levels of tampering via chewing, drinking/dissolving, smoking, and snorting reformulated oxycodone than found in this study. These initial findings suggest that the tamper-resistant controlled extended-release oxycodone has been successful at reducing, although not necessarily eliminating, tampering with this product.

There was significant diversity in the amount of time for preparation and the methods adopted. Findings from in vitro laboratory assessment of the tamper resistant properties of reformulated oxycodone that are informed by real-world tampering reports or potential scenarios suggest that more time and tools are required to extract the active opioid ingredient as compared to the original formulation (Cone et al., 2013). There was evidence that people are not always successful on the first attempt or successful at all given the number reporting multiple attempts. As noted by Cone et al. (2013), individuals who are motivated to tamper with opioids might develop the means of doing so through repeat attempts, and with sufficient time and resources. Participants in the current study reported that experimentation was the main way they learnt to tamper, with word-of-mouth through friends the next primary route for information. Internet exchange regarding tampering with prescription drugs is common, with information on numerous methods for tampering available with varying levels of accuracy and detail (Cone, 2006); and such exchanges are often in the context of harm reduction purposes in relation to use (Nielsen & Barratt, 2009). Despite the perceived ubiquity of information available on the internet, and the demonstrated presence of feasible manipulation techniques

Table 4
Attractiveness ratings by NOMAD participants who injected original and reformulated oxycodone ($n = 19$).

Attractiveness items[a]	(A) Original formulation injection (past month; Wave 1)		(B) Original formulation injection (past month; Wave 2)		(C) Reformulation injection (past month; Wave 2)		A (ref) versus B OR (95% CI) [b]	B (ref) versus C OR (95% CI) [b]
	% agree	*n*	% agree	*n*	% agree	*n*		
I would definitely tamper with the oxycodone product	84 (62–95)	16	79 (57–92)	15	53 (31–74)	9	0.70 (0.11–4.38)	0.30 (0.08–1.12)
The oxycodone product is unpleasant to use (tamper)	16 (6–38)	3	5 (1–25)	1	50 (28–72)	8	0.30 (0.03–3.49)	33.00 (1.69–643.09)**
The oxycodone product is difficult to inject	0 (0–17)	0	0 (0–17)	0	47 (25–70)	7	1.00 (0.06–17.17)	27.35 (1.40–534.22)**
The oxycodone product is painful to inject	0 (0–17)	0	11 (3–31)	2	40 (20–64)	6	5.57 (0.31–99.09)	5.67 (1.28–25.12)*
The oxycodone product contains fillers than cause safety issues	74 (51–88)	14	63 (41–81)	12	93 (70–99)	14	0.61 (0.24–1.58)	8.17 (0.73–91.06)
The oxycodone product is easy to cut up	79 (57–92)	15	79 (57–92)	15	21 (8–48)	3	1.00 (0.29–3.46)	0.07 (0.01–0.59)*
The oxycodone product is easy to dissolve#	67 (44–84)	12	74 (51–88)	14	14 (4–40)	2	1.40 (0.50–3.92)	0.06 (0.01–0.46)**

[a] The sample is restricted to those participants who had injected original oxycodone in the month prior to Wave 1 and who had injected original and reformulated oxycodone in the month prior to Wave 2. Note that only 17 participants responded to 'I would definitely tamper with the oxycodone product' for B and C, 16 participants responded to 'The oxycodone product is unpleasant to use' for B and C, 15 participants responded to 'The oxycodone product is difficult to inject/painful to inject/contains fillers that cause safety issues' for B and C, and 14 participants responded to 'The oxycodone product is easy to cut up/dissolve' for B and C.

[b] Odds ratios (OR) are presented here with 95% confidence intervals (95% CI); an odds ratio of 1 indicates the event is equally probable at each time point, >1 indicates the item was endorsed by more people regarding the non-reference category compared to the reference category, and <1 indicates the item was endorsed by fewer people regarding the non-reference category compared to the reference category. OR: odds ratio; 95% CI: 95% confidence interval.

* $p < 0.050$.

** $p < 0.010$.

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(Boyce & Hoag, 2014), fewer than one-fifth (15%) of the reported methods in the present study were based on internet sources. This in itself may reduce the potential for harm to the consumer: McNaughton et al. (2014) reported only a small number of posts identifying preparation methods for tampering post-introduction; only 9% of posts related to potentially feasible manipulation techniques.

There were few distinguishing characteristics of those who tampered with the reformulated oxycodone compared with those who tampered only with the original oxycodone formulation, with similar socio-demographic profiles, mental and physical health, and, most importantly, levels of pharmaceutical opioid dependence. The key difference between the two groups was that those participants who reported tampering with reformulated oxycodone had greater access to the product, in that they were more likely to be prescribed oxycodone. Contrarily, this group was also identified by a greater likelihood of reporting stealing pharmaceutical opioids, even after controlling for other predictors, such as licit use of oxycodone. This group also had higher engagement in OST, which could suggest that drug treatment may have a protective mechanism although this variable did not remain a significant predictor of group membership after controlling for demographics and other significant predictors of tampering. We did not find evidence to suggest a higher level of drug-related harms among those who tampered with the new formulation (these were not harms specific to oxycodone use).

The present study indicated lower ratings of attractiveness for reformulated oxycodone for the few participants who had tampered with original and reformulated oxycodone post-introduction. These conclusions are tentative, as only 19 participants had tampered with the original product (Wave 1 and 2) and reformulated product (Wave 2). However, most of the participants who had injected both formulations were concerned that the new formulation had considerable excipients which might increase risk of harm, and reported that reformulated oxycodone was more difficult to cut up and dissolve. Lower ratings of attractiveness provide early support for the inclusion of tamper-resistant formulations as one part of the broader strategy to reduce prescription opioid tampering and misuse (Australian Government, 2012; US Department of Health and Human Services et al., 2013). However it is important to note that introduction of these products should be set within a broader context of change, including better clinical practice and systems (e.g., Fishman, Papazian, Gonzalez, Riches, & Gilson, 2004; Manchikanti et al., 2012; Reifler et al., 2012), and greater treatment access for individuals who may be impacted by these changes and wish to engage with these services, especially while other substances and formulations of product that are not resistant to tampering are available (Lionberger, 2014).

Strengths and limitations

This study is the first post-marketing surveillance study of controlled-release oxycodone in Australia, and this paper is the first to examine detailed methods of tampering among an Australian cohort. US studies have examined levels of tampering (Butler et al., 2013) and perceived attractiveness (Sellers et al., 2013). Whilst there has been analysis of internet posts regarding methods for tampering (McNaughton et al., 2014, this study represents, to the author's knowledge, the first in-depth systematic investigation of self-reported methods of tampering and their perceived success. The high retention rate for Wave 2 interviews, comprehensive assessment of pharmaceutical opioid tablet forms and sizes, and emphasis on confidentiality and anonymity are strengths of this study. Data were based upon self-report however evidence points to sufficient validity and reliability of self-report in studies assessing pharmaceutical opioid (Passik, Hays, Eisner, & Kirsh, 2006) and illicit drug use (Darke, 1998). Wave 2 interviews were conducted during the transition period between sales of original and reformulated oxycodone, although prescription sales data indicated a quick transition (Degenhardt et al., 2014). Findings could reflect early adjustments in drug market; extending monitoring of the cohort (Wave 3 12-month follow-up) will clarify whether these findings represent stable changes in patterns of use. This study is also limited by the number of comparisons made between groups. To account for this concern, we have reported effect sizes and 95% confidence intervals for odds ratio to indicate magnitude of effect rather than focusing on statistical significance.

Conclusions

Initial findings from this prospective cohort suggest lower ratings of attractiveness for a tamper-resistant formulation of controlled-release oxycodone compared to a non-tamper resistant formulation. In accordance, low level of use and tampering with reformulated oxycodone were evident; those who did tamper with reformulated oxycodone generally only used the product on one occasion. Although this reformulated oxycodone does objectively appear to exert a deterrent effect on tampering, the present study did not indicate elimination of tampering with the oxycodone. Development of abuse-deterrent technologies is a current public health strategic priority; continued introduction of these products into the market means that appropriate, effective treatment options must be available, particularly given high rates of pharmaceutical opioid dependence amongst this group.

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Conflict of interest

BL, and LD have received untied educational grants from Reckitt Benckiser for the post-marketing surveillance of opioid substitution therapy medications in Australia, the development of an opioid-related behavior scale, and a study of opioid substitution therapy uptake among chronic non-cancer pain patients.

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