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HEALTH HARMS OF NON-MEDICAL PRESCRIPTION OPIOID USE: A SYSTEMATIC REVIEW

Daniel Werb, PhD[1,2] **[Assistant Professor]**, **Ayden Scheim, PhD**[2,3] **[Assistant Professor]**, **Ayorinde Soipe, MSc**[4,5] **[Clinical Fellow]**, **Samantha Aeby, MSc**[6] **[Research Associate]**, **Indhu Rammohan, BSc**[2] **[Research Assistant]**, **Benedikt Fischer, PhD**[7,8,9,10] **[Professor]**, **Scott E. Hadland, MD**[11,12] **[Assistant Professor]**, **Brandon D. Marshall, PhD**[4] **[Associate Professor]**

[1.] Division of Infectious Diseases & Global Public Health, University of California San Diego, San Diego, USA

[2.] Centre on Drug Policy Evaluation, St. Michael's Hospital, Toronto, Canada

[3.] Department of Epidemiology and Biostatistics, Dornsife School of Public Health, Drexel University, Philadelphia, USA

[4.] Department of Epidemiology, Brown University School of Public Health, Providence, USA

[5.] Division of Nephrology, Department of Medicine, State University of New York, New York, USA

[6.] Institute for Mental Health Policy Research, Centre for Addiction and Mental Health, Toronto, Canada

[7.] Schools of Population Health & Pharmacy, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealnad

[8.] Department of Psychiatry, University of Toronto, Toronto, Canada

[9.] Centre for Applied Research in Mental Health and Addiction, Simon Fraser University, Vancouver, Canada

[10.] Department of Psychiatry, Federal University of Sao Paulo, São Paulo, Brazil

[11.] Grayken Center for Addiction and Department of Pediatrics, Boston Medical Center, Boston, USA

[12.] Division of General Pediatrics, Department of Pediatrics, Boston University School of Medicine, Boston, USA

Abstract

Correspondence to: Dr Dan Werb, PhD, Director, Centre on Drug Policy Evaluation, Li Ka Shing Knowledge Institute, St. Michael's Hospital, 209 Victoria St, Toronto, ON, Canada M5B 1T8**; Tel:** 647-838-9372 daniel.werb@unityhealth.to.

Author contributions: DW and BDM conceptualised the study, led the systematic review process and drafted the manuscript. AIS contributed substantially to leading the systematic review process. AS, SA, IR carried out the systematic review process. SAH, AIS and BF contributed substantially to the conceptual and methodological aspects of the manuscript. All authors contributed to the final manuscript text.

Issues: Non-medical prescription opioid use (NMPOU) contributes substantially to the global burden of morbidity. However, no systematic assessment of the scientific literature on the associations between NMPOU and health outcomes has yet been undertaken.

Approach: We undertook a systematic review evaluating health outcomes related to NMPOU based on ICD-10 clinical domains. We searched 13 electronic databases for original research articles until 1 July 2021. We employed an adaptation of the Oxford Centre for Evidence-Based Medicine 'Levels of Evidence' scale to assess study quality.

Key Findings: Overall, 182 studies were included. The evidence base was largest on the association between NMPOU and mental and behavioural disorders; 71% (129) studies reported on these outcomes. Less evidence exists on the association of NMPOU with infectious disease outcomes (26; 14%), and on external causes of morbidity and mortality, with 13 (7%) studies assessing its association with intentional self-harm and 1 study assessing its association with assault (<1%).

Implications: A large body of evidence has identified associations between NMPOU and opioid use disorder as well as on fatal and non-fatal overdose. We found equivocal evidence on the association between NMPOU and the acquisition of HIV, hepatitis C and other infectious diseases. We identified weak evidence regarding the potential association between NMPOU and intentional self-harm, suicidal ideation and assault.

Discussion and Conclusions: Findings may inform the prevention of harms associated with NMPOU, though higher quality research is needed to characterise the association between NMPOU and the full spectrum of physical and mental health disorders.

Keywords

prescription drugs; opioid overdose; health outcomes; non-medical; systematic review

INTRODUCTION

The use of naturally-occurring, synthetic and semisynthetic opioids is common worldwide, with methadone, morphine and fentanyl all included on the World Health Organization's List of Essential Medicines [1]. Strong evidence suggests that opioids are effective in the treatment of acute and cancer-related pain [2], though little evidence their use for chronic non-cancer pain exists, particularly in the long-term [3]. Nevertheless, rates of opioid prescribing increased precipitously in the United States and Canada over the past two decades [4,5]. In the United States and Canada, the increased availability of prescription opioids has contributed to a high prevalence of non-medical use: in 2015, for example, 12.5 million people in the United States engaged in non-medical prescription opioid use (NMPOU) amounting to 4.7% of the population [6]. This is of concern given that NMPOU is a primary driver of the opioid overdose epidemic affecting North America [5,7].

To date, efforts to respond to and reduce the health impacts of NMPOU have focused largely on its contribution to overdose risk [8]. However, the range of health harms associated with NMPOU remain poorly synthesized (e.g. only one scoping review on the topic exists [9]), despite a large evidence base spanning multiple scientific and clinical disciplines. This is

of public health and public policy concern, given that clinicians, implementation scientists and policymakers require a comprehensive assessment of potential harms to inform clinical practice, interventions and policy responses.

We therefore conducted a systematic review of the scientific literature to assess the known associations between NMPOU and a range of clinical outcomes.

METHODS

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. We searched electronic literature databases, listed in Table S1 (Supporting Information), for articles published as of 1 October 2018. We defined NMPOU as: use in the context of someone else's prescription or the use of one's own prescription outside of prescribed parameters (i.e. dose, frequency, mode of consumption or indication) [11]. We used International Classification of Diseases, 10th revision (ICD-10) for physical and mental health disorders potentially associated with NMPOU, using relevant Medical Subject Headings (MeSH) and keywords (see Table S1). Table 1 lists ICD-10 codes potentially associated with non-medical prescription opioid use. Hand searching of relevant academic meetings and reference lists was also done. All searches were conducted between 24 October 2015 and 15 October 2018.

Eligible studies were: (i) peer-reviewed; (ii) measured current or past NMPOU; and (ii) were a randomised control trial, case-control, comparison study, cohort study, non-randomised trial, quasi-experimental study, time-series analysis or ecological study. Studies were excluded if they failed to isolate NMPOU, did not capture ICD-10 outcomes and were not written in English. Two of four investigators independently reviewed titles and abstracts in stage 1, and full texts in stage 2, classifying studies as "potentially relevant" or "irrelevant". Disagreements were resolved by consensus.

We employed the Oxford Centre for Evidence-Based Medicine 'Levels of Evidence' [12] to assess the contribution of each study to the scientific evidence base. The 'Levels of Evidence' tool provides a rank based on study design, with studies designed to provide a higher level of evidence ranked lower (i.e. the highest rank is 1; the lowest is 5). For the current study, we adapted the tool to range from 1 to 4; this was done given that studies with the lowest level of evidence based on the tool (ranked at 5, and consisting of non-data driven expert opinion) were not eligible for inclusion in the systematic review because they did not present data. Two investigators independently scored studies, with a third author verifying, and consensus achieved where needed by a fourth author. Assessments of the level of evidence within the 1-4 range were not a basis for exclusion.

RESULTS

Study selection and characteristics

Overall, as shown in Figure 1, 11,810 studies were identified, yielding 285 full text articles assessed for eligibility, with 103 excluded. Ultimately, 182 studies met the inclusion criteria; three studies only included event count and not participant sample size [13-15].

A total of 53 (29%) studies employed cross-sectional, population-based and nationally representative observational designs [7,14,16-64]; 13 (7%) employed longitudinal, cohort-based observational designs [65-77]; 4 (2%) employed case control designs [78-81]; 6 (3%) were randomised control trials [82-87]; 54 (30%) employed cross-sectional data from convenience samples [73,88-140]; 10 (5%) employed longitudinal (including repeated cross-sectional) data from nationally representative studies [15,17,141-147]; and 42 (23%) retrospectively assessed individual-level data [13,37,148-187]. As shown in Figure 2, the majority of studies presented data from the USA (126, 69%). Other countries represented included Canada (22, 12%), Australia (13, 7%), France (4, 2%), India (4, 2%), Nordic countries (4, 2%), China (3, 2), the United Kingdom (2, 1%), Estonia (1, <1%), Iran (1, <1%) and Israel (1, <1%).

Levels of evidence assessment

The mean assessment score was 3.30 (SD = 1.01; interquartile range = 2-4), reflecting that the studies included in the systematic review generally used designs that provided a lower level of evidence. Seven studies (4%) received a score of 1 (the highest score); 53 (29%) received a score of 2; 7 (4%) received a score of 3; and 115 (63%) received a score of 4 (the lowest score). We detected no significant association between study quality and year of publication ($R^2 = > -0.01$, $P > 0.05$), suggesting no significant change in quality over time.

Results of individual studies

Table 2 presents results from all eligible studies classified by ICD-10 code. As can be seen, studies investigated the association between NMPOU and outcomes across eight major clinical domains. The median number of studies investigating each clinical outcome was 15.0 (interquartile range 3.0-23.5).

Overall, the evidence base was largest with respect to the association between NMPOU and ‘mental and behavioural disorders’ with over half of all studies (129; 71%) reporting on these outcomes. The second highest quantity of evidence existed for the association between NMPOU and ‘injury, poisoning, and certain other consequences of external causes’, with 44 studies (24%) reporting specifically on fatal and non-fatal overdose. Conversely, evidence was limited for the association between NMPOU and ‘external causes of morbidity and mortality’, with only 13 studies (7%) assessing its association with intentional self-harm and only 1 study assessing its association with assault (<1%). Outcomes that were investigated by a higher than average number of studies were ‘Viral hepatitis (HCV [hepatitis C virus] and HBV [hepatitis B virus])’ (18; 10%), ‘Human Immunodeficiency Virus (HIV)’ (8; 4%), ‘Symptoms and signs involving cognition, perception, emotional state and behavior’ (17; 9%) and ‘General symptoms and signs’ (22; 12%).

B15 – B24: Viral hepatitis (Hepatitis B and C) and HIV—Studies assessing viral hepatitis infection (ICD-10 B15-B19; $n = 18$) found mixed results. Specifically, three studies found no association between NMPOU and hepatitis B or hepatitis C transmission [106,120,127], while one study by Patra *et al.* found that participants who reported exclusively injecting PO were significantly less likely to be HCV-seropositive compared to participants that injected other substances [118]. While the number of studies investigating

HIV transmission (ICD-10 B20-B24) and NMPOU was small (n = 8, 4%), the evidence was equivocal, with 3 studies (38%) reporting no association between NMPOU and HIV transmission [22,106,153], two studies (25%) reporting that exclusive NMPOU was associated with a reduced odds of HIV acquisition compared with participants that used other drugs [84,96], and two studies (25%) reporting that fentanyl injection was associated with a significantly increased risk of testing positive for HIV [44,104].

F10-F19: Mental and behavioural disorders due to psychoactive substance use—Among the 35 studies reporting on mental and behavioural disorders due to psychoactive substance use (see Table 1, Section V), there was agreement (20/20; 100%) regarding an association between NMPOU and concurrent or subsequent opioid use disorder (OUD), dependence or withdrawal. Among this subgroup of studies, 7 (35%) identified those engaging in NMPOU as specifically having a higher risk of experiencing substance use disorders compared to users of other drugs (including street opioids). For example, Miller *et al.* found that among patients discharged from a detoxification unit East Lansing, Michigan (n = 534), those that reported prescription opioid use had a signfiicantly higher odds of also reporting a medical diagnosis (adjusted odds ratio = 3.47, P < 0.05) [152].

F30 – F39: Mood [affective] disorders—Further, 27 studies (15%) examined the association between NMPOU and depressive symptomatology. An association between NMPOU and depression was reported across the vast majority of papers (>95%) examining clinical outcomes related to mood or affective disorders (ICD F30-F39). For example, Ali *et al.* (2015) found that among adolescents enrolled in the National Survey on Drug Use and Health between 2008 and 2012 (n = 84,800, mean age 14.5 years), those that engaged in NMPOU were 33% more likely to report a major depressive episode [23]. Four of the 13 studies (31%) examining neurotic, stress-related and somatoform disorders (ICD-10 F40-F48) investigated associations between NMPOU and post-traumatic stress disorders and all identified significant associations [7,25,109,125]. One study from Becker *et al.* [34] found that reporting past year NMPOU was significantly associated with reporting symptoms of panic and phobia among National Survey on Drug Use and Health respondents (n = 6,879; both adjusted odds ratios = 1.2, P < 0.05). Ten studies (5%) assessed the relationship between NMPOU and anxiety, with 7 (70%) identifying a significant association [7,33,113,126,129,137,143], two studies (20%) reporting a null finding [43,123], and one (10%) limited to reporting on the prevalence of generalized anxiety disorder (i.e. 14%) among individuals engaged in NMPOU [78].

R40-R46. Symptoms and signs involving cognition, perception, emotional state and behavior—A small subset of studies assessed the association of NMPOU with 'symptoms and signs involving cognition, perception, emotional state and behavior' (n = 16; 9%). Of note, 10 studies (63%) investigated suicidal ideation, with 7 studies reporting that NMPOU was associated with a significantly higher odds [16,21,39,41,48,138,146], and one study by Bohnert *et al.* reporting no significant association between NMPOU and suicidal ideation [133]. Only two studies (1%) investigated associations between NMPOU and aggression; one study of youth found that NMPOU was associated with intimate partner violence though not with other forms of violence [68], while another study found that

NMPOU was associated with higher scores on the Aggressive Behavior Sub-Scale of the Child Behavior Checklist [46].

R50-R69: General symptoms and signs—There was scant evidence on the direct association between NMPOU and pain. Indeed, only three studies investigated this topic, undertaken in the USA (Michigan: $n = 2050$ high school students; and southeastern New England: $n = 328$ primary care patients) and Australia ($n = 141$ participants in opioid substitution programs in Sydney and Newcastle); none identified a significant association between NMPOU and pain [69,102,130]. However, one study by Blanco *et al.* reported that, among adults enrolled in the US National Epidemiologic Survey on Alcohol and Related Conditions ($n = 34{,}653$), reporting pain in the first wave of data collection was significantly associated with NMPOU in the subsequent wave (adjusted odds ratio = 2.17, $P < 0.05$) [145].

T36 – T50: Poisoning by drugs, medicaments, and biological substances—All of the 44 studies reporting on injury and poisoning reported on poisoning by drugs, medicaments and biological substances (ICD T36–T50); specifically, opioid overdose. NMPOU was found to be significantly associated with prior, subsequent and a lifetime history of non-fatal opioid overdose, with 13 studies (3%) reporting specifically on overdose-related mortality; this included analyses of population time trends in the United States undertaken by Calcaterra *et al.* and the US Centers on Disease Control indicating increases in the opioid overdose mortality rate since 1990 [167,169].

DISCUSSION

We report the findings of a systematic review that found voluminous and consistent evidence of an association between NMPOU and OUD, as well as on fatal and non-fatal overdose. Strong evidence supported an association between NMPOU and some mental disorders, particularly depression, consistent with previous reviews in this area [188]. A smaller set of studies reported equivocal evidence on the association between NMPOU and HIV and hepatitis transmission. Finally, only scant evidence was identified on the association between NMPOU and intentional self-harm, suicidal ideation and assault.

The results of this systematic review provide further confirmatory evidence that NMPOU is implicated in the high incidence of overdose-related morbidity and mortality observed in North America. However, despite a large body of scientific literature assessing the influence of injection drug use on a range of health and social harms [189,190], the current review highlights the paucity of evidence demonstrating that injection NMPOU is associated with a higher risk of HIV or HCV transmission compared with the injection of other drugs. Collectively, these findings have important implications for policy and practice. First, while they confirm that interventions to prevent overdose should be tailored specifically to NMPO-using subpopulations, they suggest that efforts to prevent transitions into injection drug use and the disease transmission risk that often follows should be tailored to a broader range of subpopulations beyond those engaging in non-injection NMPOU. For instance, data from multiple North American settings has demonstrated that crystal methamphetamine is the drug primarily implicated in injection initiation events [191,192]; furthermore,

injection cocaine use is an identified risk factor for disease transmission (likely related to its short half-life) [193]. Given the heterogeneous distribution of injection-related risks among subpopulations, ensuring that frontline harm reduction and related health services are appropriately tailored to those at greatest risk is needed to reduce injection-related morbidity and mortality.

Given the established link between NMPOU and OUD, and that opioid agonist therapies (OAT) are recognised as the gold standard for management of OUD [194], expanding access to patient-oriented OAT modalities should be prioritised by treatment systems in North America and other settings experiencing heightened opioid-related overdose mortality. Indeed, the United States has lagged behind other settings (e.g. Western Europe) in achieving appropriate coverage of OAT such as methadone and buprenorphine, with only an estimated 15 per 100,000 PWID in the United States that access OAT [195], compared with 90 per 100,000 PWID in France [196]. Beyond coverage, recent advances have been made in Canada in refining clinical guidelines for the provision of OAT for OUD in light of the extensive evidence base on this subject as well as the increasingly diverse set of pharmacological tools used in OAT [197]. Further, there is a need to expand access to harm reduction interventions to support low-threshold entry into treatment for structurally vulnerable subpopulations engaging in NMPOU and/or with OUD (i.e. street-involved youth and individuals experiencing homelessness); this is in line with technical guidelines jointly developed by the UN Office on Drugs and Crime, the Joint United Nations Programme on HIV/AIDS, and the World Health Organization to reduce harms associated with the use of opioids and other illegal drugs [198]. To address the disproportionate burden of overdose mortality among populations engaging in NMPOU, expanded distribution of naloxone (an opioid antagonist used to reverse opioid overdose events) and the implementation of supervised consumption sites should be undertaken, given the high level of evidence demonstrating their effectiveness in overdose prevention [199,200]. These should be coupled with syringe services programs, given their cumulative impact on reducing infectious disease transmission among people who use NMPOU by injection [201].

The findings of this review also suggest future directions for research. While a consensus exists regarding the association between NMPOU and overdose, less is known regarding the relationship between its use and psychiatric conditions such as anxiety disorders. While six studies assessed the association between these conditions, findings were equivocal, and the direction of causality in all studies was not determined. This suggests the potential that NMPOU is intensified by anxiety, symptomatic of anxiety, or both; alternately, given that only a minority of studies (2/6; 33%) identified a significant association between anxiety and NMPO use, alternative pathways may be present. While outside the scope of this review, evidence suggests that the endogenous opioid system may mediate the association between opioid use and psychiatric comorbidities via variation in resting levels of endogenous opioids (i.e. individuals with lower resting levels may be at higher risk of developing psychiatric comorbidities or symptoms) [202]. Delineating the complex links between these conditions is particularly important in light of a recent meta-regression analysis that estimated the global prevalence of anxiety disorders at 7.3% [203], with individuals having experienced conflict and those in rural settings at significantly greater risk of experiencing anxiety disorders. If, as the results of this systematic review imply,

anxiety disorders are associated with NMPOU, increasing access to OAT may, beyond its capacity to reduce the severity of OUD, also address key risk factors for the initiation or continuation of NMPOU, including co-morbid mental health conditions. That is because retention in OAT has been shown to be significantly associated with a subsequent reduction in the severity of psychiatric comorbidities among individuals experiencing both OUD and psychiatric comorbidities [204]. Importantly, the inverse approach (i.e. treating psychiatric comorbidities prior to enrolment in OAT) was not shown to be significantly associated with reductions in OUD severity [204].

This study has limitations. First, while we restricted the systematic review to scientific peer-reviewed literature, we did so in an effort to ensure a standard of scientific rigor commensurate with clinical practice and the development of effective policy; however, this resulted in the exclusion of potentially important 'gray literature' findings. Relatedly, we restricted to studies that assessed clinical outcomes that fell within ICD-10 classifications, which was done to improve the clinical relevance of this systematic review, but which likely resulted in additional health outcomes related to NMPOU not being captured. Second, it is possible that certain published studies were overlooked during the search, though this concern was likely mitigated by the fact that this process was duplicated, with additional verification by a third author. Third, we only assessed English-language literature because of linguistic limitations on our team; it is likely that peer-reviewed studies on the topic of NMPOU were published in other languages but not included in the review. Fourth, we did not undertake a meta-analysis as an additional step after systematic assessment of the scientific literature given the diversity of outcomes and methodologies employed by included studies, which limited meaningful meta-analytic assessment. Fifth, Although studies focused on HCV and HIV (L00-L99; 'Infections of the skin and subcutaneous tissues'), others can arise from the injection of opioids intended for oral consumption (e.g. nerve damage, foreign body pulmonary embolisation and pulmonary hypertension, thrombophlebitis, deep vein thrombosis, endocarditis, septic arthritis, osteomyelitis and septicaemia); these may also be a result of NMPOU. Finally, we assessed study quality using a standardised checklist, though author subjectivity may have influenced the quality score.

CONCLUSIONS

In sum, we report on the findings of a systematic review assessing the peer-reviewed evidence regarding clinical outcomes associated with NMPOU. We note areas of general consensus as well as those wherein evidence is equivocal, weak, or non-existent. These findings should inform current efforts to address the ongoing use of—and harms associated with—NMPOU in a range of settings internationally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINT SUMMARY

- We identified 182 peer-reviewed studies that assessed health outcomes associated with non-medical prescription opioid use until 1 July 2021
- A large body of evidence exists on the association between non-medical prescription opioid use and mental and behavioural disorders as well as on fatal and non-fatal overdose.
- Equivocal evidence exists on its association with the acquisition HIV, hepatitis C and other infectious diseases; weak evidence exists on its potential association between NMPOU and intentional self-harm, suicidal ideation, and assault
- This is the first systematic review identifying the range of health outcomes associated with non-medical prescription opioid use
- These results can support policy and clinical decision-making with respect to preventing opioid-related outcomes, and can inform efforts to bolster the evidence base on outcomes for which little data currently exist

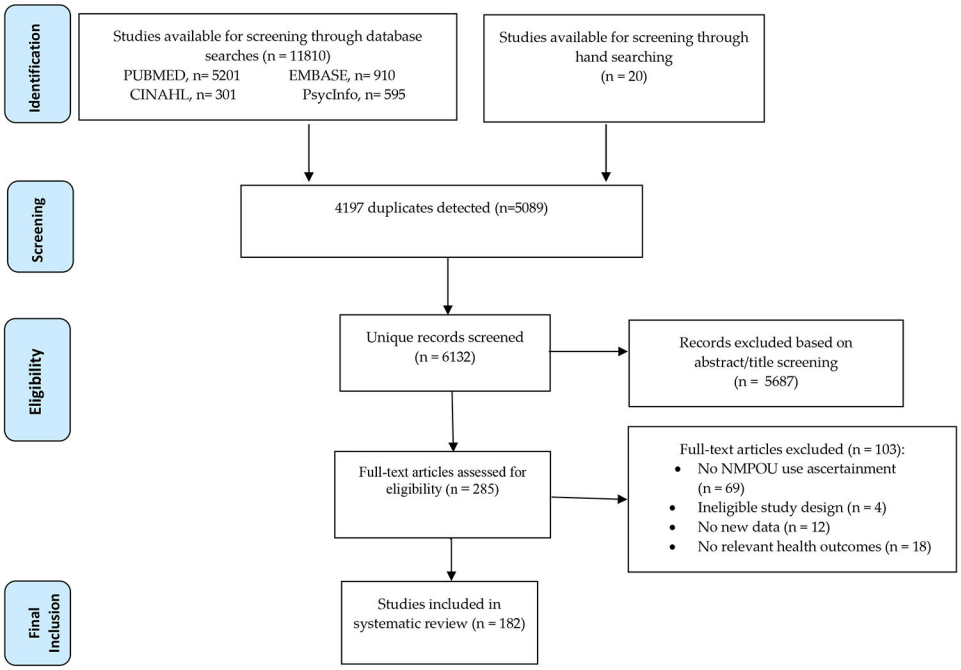

Figure 1:
PRISMA flow chart of study selection. NMPOU, non-medical prescription opioid use.

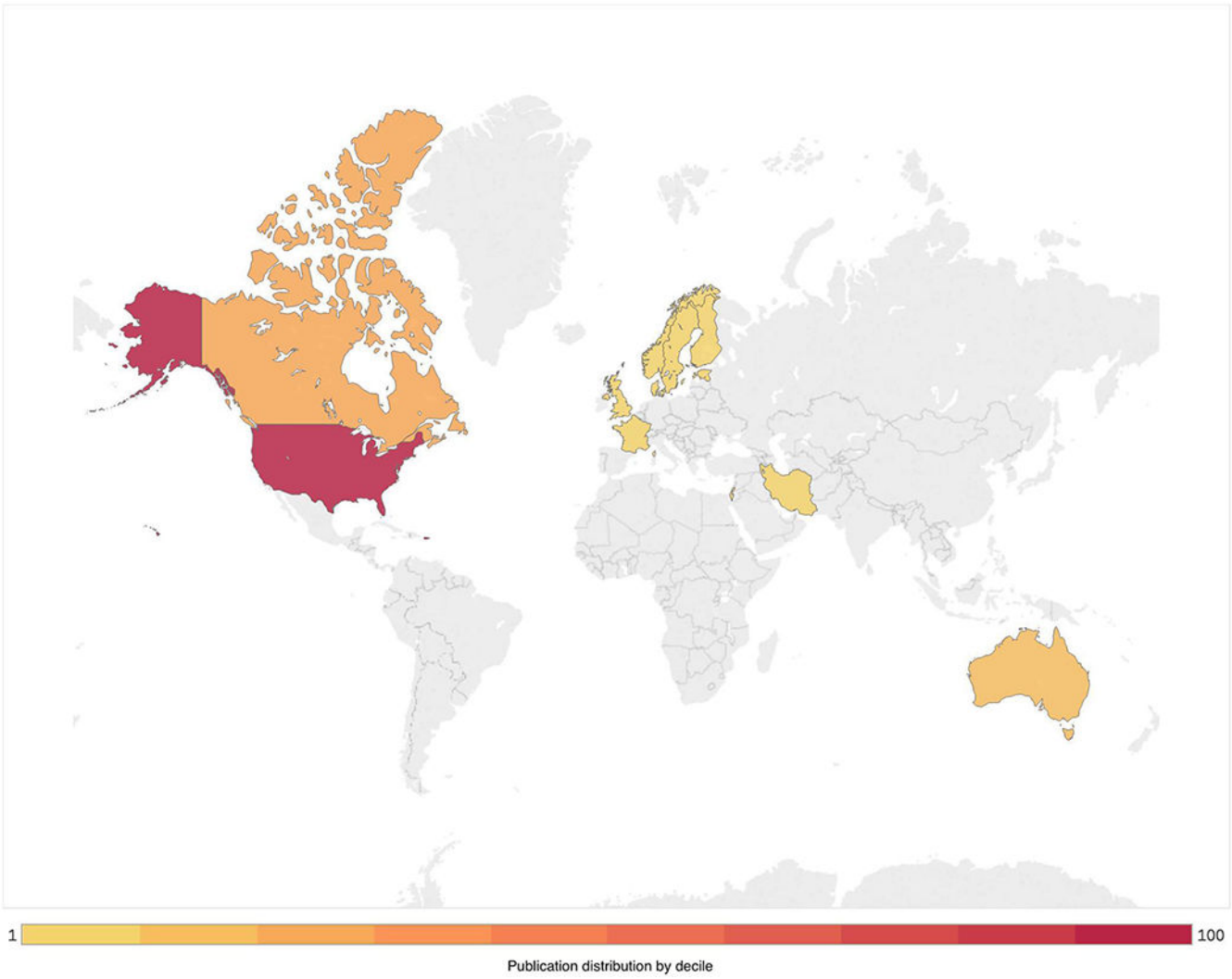

Figure 2:
Distribution of publications on clinical outcomes associated with non-medical prescription opioid use

Table 1.

International Classification of Diseases–10th revision codes potentially associated with non-medical prescription opioid use

I. Infectious diseases
B15 – B19: Viral hepatitis
B20 – B24: Human Immunodeficiency Virus [HIV]
III. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
D65 – D69: Coagulation defects, purpura and other hemorrhagic conditions
V. Mental and behavioral disorders
F10 – F19: Mental and behavioral disorders due to psychoactive substance use
F30 – F39: Mood [affective] disorders
F40 - F48: Neurotic, stress-related and somatoform disorders
F00 – F99: Other psychiatric / mental health measures
XI. Diseases of skin and subcutaneous tissue
L00 – L99: Infections of the skin and subcutaneous tissue
XVI. Certain conditions originating in the perinatal period
P05 – P08: Disorders related to length of gestation and fetal growth
P90 – P96: Other disorders originating in the perinatal period
XVIII. Symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified
R40-R46. Symptoms and signs involving cognition, perception, emotional state and behavior
R50-R69: General symptoms and signs
XIX. Injury, poisoning, and certain other consequences of external causes
T36 – T50: Poisoning by drugs, medicaments, and biological substances
XX. External causes of morbidity and mortality
X60-X64: Intentional self-harm
X85-Y09: Assault

Table 2.

Summary of 182 studies examining health outcomes of non-medical prescription opioid use, sorted by World Health Organization International Classification of Diseases (ICD 10) code [V. 2016]

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
I. Infectious and parasitic diseases **B15 – B19: Viral hepatitis [Hepatitis B]**						
Havens 2007, USA	Cross-sectional	184 prescription opioid [PO] users recruited through street outreach and snowball sampling; median age: 30 years	Injection in past 30 days	4	HBV [self-reported]	There was no significant difference in HBV infection between those who inject PO and those who did not (*P*=0.184).
Wylie 2006, Canada	Cross-sectional 2003-2004	369 PWID recruited through street outreach	Injection in past 6 months 6 months	4	HBV serostatus [IMX HBV core IgG]	Morphine injection was not significantly associated with HBV serostatus (OR=1.2 [0.7–1.8]); overall HBV prevalence was 30%.
B15 – B19: Viral hepatitis [Hepatitis C]						
Aitken 2008, Australia	Cross-sectional 2005-2006	316 street-recruited PWID	Injection drug use in previous 3 months	4	HCV serostatus	There was no significant difference between buprenorphine injectors and non-injectors in prevalence of HCV antibody (OR=1.2 [0.5-3.0]) or ribonucleic acid (OR=0.95 [0.4-2.1]).
Barry 2011, USA	Cross-sectional 2006	4122 veterans in the third wave of a follow-up survey, median age: 52 years	Past-year use of NMPOU	4	HCV	Veterans in care have a high prevalence of NMPOU which was associated with hepatitis C (AOR=1.5 [1.2-1.9]); HCV prevalence: 56.8%
Bruneau 2012, Canada	Prospective 2004-2009	246 HCV-negative PWID at baseline; mean age: 34.5 years	Past month injection drug use	2	HCV infection [EIA test]	Compared to non-PO injectors, PO injectors were more likely to become infected with HCV (aHR 1.87 [1.16-3.03]).
Chelleng 2008, India	Cross-sectional 2004-2005	143 PWIDs including female sex workers; median age: 24.7 years	Injection drug use in previous 6 months	4	HCV antibodies prevalence [ELISA]	Prevalence of anti-HCV antibodies was significantly lower among exclusive PO injectors compared to exclusive heroin injectors [n=13/31] vs 85.2% (41.9% [n=23/27]], p<0.05).
Das 2007, India	Cross-sectional	254 PWIDs randomly sampled and enrolled; median age: 26 years	Injection drug use in previous 6 months	4	HCV serostatus [EIA]	Prevalence of HCV significantly lower among exclusive PO injectors compared to exclusive heroin injectors (23.9% [n=27/113] vs 45.4% [5/11], *P* <0.05).
Hadland 2014, Canada	Prospective 2005-2011	940 adolescents and young adults aged 14–26 recruited through street-based outreach and snowball sampling; mean age: 21.7 years	Substance use in past 6 months (injecting, non-injecting)	2	HCV serostatus and seroconversion	PO injection was significantly and positively associated with HCV serostatus at baseline (OR=8.69 [5.01-15.1]), after covariate adjustment PO injection was not positively associated with HCV seroconversion (aHR=0.94 [0.40-2.21])
Han 2017, USA	Cross-sectional 2015	51200 respondents in the 2015 NSDUH identified as prescription opioid users	Lifetime and past-year NMPOU	4	HBV or HCV	Among adults with prescription opioid misuse, prevalence of HBV or HCV was 12.4% (95% CI, 8.32-18.19)

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Havens 2007, USA	Cross-sectional	184 prescription opioid [PO] users recruited through street outreach and snowball sampling; median age: 30 years	PO injection in past 30 days	4	HCV [self-reported]	More people who inject PO self-reported HCV compared to those who did not inject PO, (n=9 [14.8%] vs. n=2 [1.7%], $P<0.05$)
Havens2013, USA	Cross-sectional 2008-2010	392 PWIDs recruited through street outreach median age: 31 years	Past month (any drug use), lifetime (injection)	4	HCV [home access test]	Injecting prescription opioids was significantly associated with HCV seropositivity (AOR=2.22 [1.13-4.35]); prevalence of HCV infection was 54.8%
Iversen 2010, Australia	Cross-sectional 1998-2008	15,852 PWID recruited from needle and syringe programs; mean age: 31 years	Number of years injecting NMPOU	4	HCV serostatus [EIA test]	For those injecting ≤ 4 years, injection of methadone or buprenorphine (female: AOR=4.78 [2.63-8.70]; male: AOR=3.06[1.58-5.92]), and injection of other prescription opioids (women: AOR=2.20 [1.24-3.90]; men: AOR=1.77 [1.03-3.04]), were associated with HCV positive serostatus
Lankenau 2015, USA	Cross-sectional 2009-2011	162 PWIDs sampled in New York and Los Angeles; mean age: 21.4 years	Lifetime NMPOU injection	4	HCV [self-reported]	Lifetime prescription opioid injectors were nearly 3 times more likely to report being HCV positive than non-prescription opioid injectors (AIRR=2.69 [1.07-6.78], $P<0.05$)
Mahanta 2009, India	Cross-sectional 2004-2006	398 PWIDs recruited from drop-in centres; median age: 26 years	Injection NMPOU in previous 6 months	4	HCV serostatus [EIA]	Proxyvon-only injection was associated with reduced odds of HCV infection (AOR=0.42 [0.24-0.71]
Patra 2009, Canada	Prospective 2004-2005	582 participants from the most recent follow-up in the OPICAN study; mean age:35.2 years	NMPOU use in past 30 days	4	HCV [self-reported]	Among participants who primarily used prescription opioids, risk of HCV positivity was low (OR=0.35 [0.12-1.01]); self-reported HCV prevalence was 24%
Powell 2019, USA	Ecological 2004-2015	50 US states	Past-year median OxyContin misuse rate	2	HCV incidence rate	States with above-median OxyContin misuse before the reformulation experienced a 222% increase in HCV infection rates vs. 75% increase in states with below-median OxyContin misuse
Wylie 2006, Canada	Cross-sectional 2003-2004	369 PWID recruited through street outreach	Injection NMPOU in previous 6 months	4	HCV serostatus [AxSYM HCV]	Morphine injection was not significantly associated with HCV serostatus (OR=1.2 [0.8-1.9]); overall HCV prevalence was 53.7%
Zibbell 2014, USA	Cross-sectional 2012	123 PWID recruited using snowball sampling	Injection NMPOU in previous in past year	4	HCV serostatus [PCR]	Prescription opioid injection was significantly associated with HCV positivity (AOR=5.53 [1.92-15.91])
B20 – B24: HIV						
Barry 2011, USA	Cross-sectional 2006	4122 veterans in the third wave of a follow-up survey; median age 52 years	Past year NMPOU	4	HIV	Veterans in care have a high prevalence of NMPOU which was not associated with HIV status; HIV prevalence was 60%
Buttram 2014, USA	Clinical trial 2008-2010	515 MSM participating in a risk reduction intervention trial; mean age: 38.9 years	Past year and past 90 days injection NMPOU	2	HIV	Prescription opioid misuse in past 90 days was associated with lower odds of HIV-positive serostatus (OR=0.825 [0.553-1.232]); HIV seropositive prevalence: 48.5%
Black 2013, USA	Cross sectional 2007-2011	29,459 PO users recruited from 540 treatment facilities; mean age=33.1 years	Past 30 days NMPOU	4	HIV/AIDS prevalence [ASI-MV]	Prescription opioid injection was not significantly associated with increased odds of HIV/AIDS (OR=1.05 [0.73-1.51; 1.1% reported a positive HIV/AIDS test

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Conrad 2015, USA	Cross-sectional	135 HIV positive persons in a rural Indiana county; mean age: 35 years	Lifetime NMPOU injection	4	HIV	Among 135 persons with HIV infection, 80.0% are PWIDs and inject tablets of oxymorphone as their drug of choice
Novak 2016, Denmark, Germany, Great Britain, Sweden	Cross-sectional 2014	22070 survey respondents in the European Union ages 12-49	Lifetime and past year NMPOU	4	HIV	NMPO users were more likely to be HIV positive (AOR=18.9 [10-34; P<0.001] that those not reporting NMPOU
Obadia 2001, France	Cross-sectional 1997	343 PWIDs recruited at 32 pharmacies, 4 needle exchange programs and 3 syringe vending machines; median age = 30 years	Injection NMPOU in previous 6 months	4	HIV	Compared to people who inject [self-reported] other drugs, buprenorphine-only injection was significantly associated with reduced odds of HIV (AOR=0.63 [0.41-0.94])
Talu 2010, Estonia	Cross-sectional	350 PWID recruited using respondent driven sampling mean age: 23.9 years	Injection NMPOU in past 28 days	4	HIV [HIV GACPAT]	Fentanyl injection was associated with increased risk of testing positive for HIV (AOR=2.89 [1.55-5.39]); HIV prevalence was 62% among fentanyl injectors (95% CI 56.97–67.03, P<0.001)
Wylie 2006, Canada	Cross-sectional 2003-2004	369 PWID recruited through street outreach	Injection NMPOU in previous 6 months	4	HIV serostatus [AxSYM HIV1/2 gO]	Morphine injection was not positively associated with HIV serostatus (OR=0.4 [0.1–1.1]); overall HCV prevalence was 7%
III. Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism D65 – D69: Coagulation defects, purpura and other haemorrhagic conditions						
CDC 2013, USA	Case-control	Cases: 15 patients with TTP-like illnesses, Controls:28 patients recruited from a methadone clinic; median age: cases= 34 years, controls= 31 years	Injection NMPOU in previous 6 months	4	TTP-like illness	The cases of TTP-like illness were associated with dissolving and injecting tablets of Opana-ER, a recently reformulated extended-release form of oxymorphone intended for oral administration; 14 of the 15 case-patients, reported recent injection of reformulated Opana-ER (OR= 35.0 [3.9–312.1])
V. Mental and behavioural disorders F10 – F19: Mental and behavioural disorders due to psychoactive substance use						
Adams 2006, USA	Prospective	11352 patients with chronic pain taking prescription opioids	Past year NMPOU	2	Withdrawal [withdrawal score]	Withdrawal score of hydrocodone was significantly higher than that of tramadol (P<0.01)
Back 2010, USA	Cross-sectional 2006	55,279 respondents in the NSDUH	Past year NMPOU	4	Dependence [DSM IV criteria]	Among the respondents, 13.2% reported prescription opioid dependence
Back 2011, USA	Cross-sectional	24 non-treatment seeking individuals (12 men and 12 women)	Past year NMPOU	4	Dependence [DSM-IV criteria]	All recruited participants had PO dependence. The most common NMPO was with oxycontin (56%)
Barry 2011, USA	Cross-sectional 2006	4122 veterans in the third wave of a follow-up up survey; median age: 52 years	Past year NMPOU	4	Opioid use disorder	Veterans in care have a high prevalence of NMPOU which is associated with opioid use disorder [AOR 2.7 (1.9-3.9)]; opioid use disorder prevalence: 30.7%
Becker 2007, USA	Cross-sectional 2002-2004	6879 respondents in the NSDUH	Past year NMPOU	4	Dependence [DSM-IV criteria]	Of those with non-medical use, 12.9% met criteria for abuse or dependence

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Becker 2011, USA	Retrospective 2006-2008	3238 respondents in the NSDUH	Past year NMPOU	2	Dependence [self-reported]	Past-year opioid analgesic abuse and/or dependence was associated with having a physician source of opioids (AOR=2.0 [1.5-2.7]); 20.3 % of participants had PO abuse/dependence
Blanco 2016, USA	Prospective 2001-2005	34653 sample of US adults participating in NESARC	Past-year NMPOU	1	Opioid use disorder	Prospective association between pain at wave 1 predicting PO use disorder at wave 2 (AOR=2.17 [1.35-3.48]). Predicted risk of developing PO use disorder at wave 2 was 0.44% for persons without and 0.62% for those with pain interference at wave 1 (increase of 41%)
Blanco 2016, USA	Prospective 2001-2005	34653 sample of US adults participating in NESARC	Past year NMPOU	1	Opioid tolerance, withdrawal	Pain at wave 1 was significantly associated with opioid tolerance (β=0.17, *P*=0.002) and withdrawal (β=0.24, *P* <0.001) at wave 2; association approached significance for taking opioids longer or at greater doses than prescribed (β=0.12, *P*=0.07)
Boyd 2009, USA	Prospective 2001-2005	34653 sample of US adults participating in NESARC	Lifetime and past year NMPOU	1	Dependence [DSM-IV criteria]	Non-medical use (at young age) in Wave 1 was associated with higher odds of a general substance or opioid abuse/dependence disorder at Wave 2 (AOR=3.42, 95% CI 1.45, 8.07)
Buttram 2014, USA	Clinical trial 2008-2010	515 MSM participating in a risk reduction intervention trial; mean age: 38.9 years	Past year and past 90 days injection NMPOU	2	Dependence [DSM-IVR criteria]	Non-medical prescription opioid use was associated with higher odds of substance dependence (OR=2.150 [1.253-3.689]; *P*=0.005); substance dependence prevalence: 62.1%
Cohen 2010, Ireland	Cross-sectional	89 service users attending an outpatient methadone stabilisation and detoxification program	Lifetime NMPOU	4	Dependence [MAP]	Those with any history of codeine misuse were more likely to have a longer drug dependence history (*P* <0.05)
Cottler 2016, USA	Retrospective cohort 1981-1983, 2007	9985 participants in population-based sample	NMPOU more than 5 times in life	2	Alcohol abuse/ dependence	Prevalence of alcohol abuse or dependence was greater in non-medical prescription opioid users (56.9%) compared to non-PO drug users (23.1%) and non-drug users (9.0%)
Edlund 2007, USA	Cross-sectional 1996-1997	9279 participants from a nationally representative study of the US civilian population	NMPOU in past 12 months	4	Problem opioid misuse including tolerance and/or physiologic problems [CIDI]	Users of prescribed opioids had significantly higher rates of any opioid misuse (AOR = 3.07 [2.05-4.60], *P* < 0.001) and problem opioid misuse (AOR = 6.11 [3.02-12.36], *P* < 0.001)
Edlund 2010, USA	Cross-sectional 2001-2004	36,605 enrollees in HealthCore and 9651 enrollees in Arkansas Medicaid all receiving chronic opioid therapy	Past six month NMPOU	4	Dependence/abuse [ICD-9-CM]	Participants with a diagnosis of 2 or more mental health disorders prior to the period of opioid use episode had increased odds of dependence/abuse in the period following opioid use episode (HealthCore patients: AOR=2.08 [1.69-2.55]; Medicaid patients: AOR=1.70 [1.21-2.39])
Edlund 2014, USA	Cross-sectional 2000-2005	568,640 individuals with new chronic non cancer pain episode being prescribed opioids	NMPOU in the 18 months after the index date	4	Opioid use disorder [ICD-9-CM]	Individuals with pre-index mental health disorders had higher rates of opioid use disorders (AOR=3.12 [2.41-4.04], *P* <0.001)

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Ghandour 2008, USA	Cross-sectional 2002-2003	7810 respondents in the 2002-2003 NSDUH	Past year NMPOU	4	Dependence [DSM-IV]	Among past year PO users, 8.3% met criteria for opioid dependence, also individuals belonging to the highest latent class had high probabilities of endorsing each of the seven symptoms of dependence (0.70–0.99)
Han 2017, USA	Cross-sectional 2015	51,200 respondents in the 2015 NSDUH identified as prescription opioid users	Lifetime and past year NMPOU	4	Opioid use	Among adults with prescription disorder opioid misuse, prevalence of past-year PO use disorder was 16.7% (95% CI 14.8-18.49)
Humeniuk 2003, Australia	Cross-sectional 1996-1997	365 heroin users recruited through snowball sampling; mean age: 28.9 years	Injection NMPOU in last 6 months	4	Dependence [SDS scale]	Participants injecting methadone were significantly more dependent on heroin than people not injecting methadone (mean SDS scores: 8.9 vs 6.39 [F=14.5, df=1, 362, P=0.000])
Kouyanou 1997, London, UK	Cross-sectional	125 patients receiving treatment for chronic pain; mean age: 41 years	Past year NMPOU	4	Dependence/abuse [DSM-III-R]	Among the sample of chronic pain sufferers, 3.2% and 4.8% met criteria for opioid abuse and dependence respectively
Martins 2007, USA	Cross-sectional 2002-2003	7810 respondents in the 2002-2003 NSDUH	Past year NMPOU	4	Withdrawal [self-reported], Tolerance [self-reported]	Prescription opioid dependence was significantly associated with withdrawal symptoms (AOR=3.76 [2.88-4.91]) and tolerance [AOR=9.90 [7.70-12.74])
McCabe 2016, USA	Longitudinal observational 1993-2013	4072 high school seniors	Past year and past month NMPOU	2	SUD at age 35	Medical use of PO without misuse during adolescence was not associated with SUD symptoms at age, while NMPOU was (AOR=2.61 [1.88-3.61]), compared to no medical or nonmedical use
McCabe 2012, USA	Cross-sectional 2009-2010	148 middle and high school students reporting past year NMPOU; mean age: 15.2 years	Past year NMPOU	4	SUD [CRAFT]	Among past year NMPO users, 35.1% screened positive for SUD based on the craft test
Miller 2004, USA	Retrospective 2000	534 patients admitted and discharged from an addiction detoxification unit; mean age: 40.37 years	Current NMPOU	2	Substance-related diagnosis [DSM criteria]	Users of NMPOs had a higher mean number of substance-related diagnosis than non-users, also opiate dependent patients were more likely to have a medical diagnosis (OR = 3.47 [2.00-5.99])
Morasco 2008, USA	Randomised trial 2006-2007	127 patients recruited from a veteran's affairs medical centre; mean age: 59.8 years	Lifetime NMPOU	1	SUD [ICD-9-CM]	Borrowing pain medication (misuse) was significantly associated with increased odds of SUD (AOR=6.62 [1.4-30.7])
Morasco 2013, USA	Cross-sectional	80 participants with chronic pain recruited from a veteran's affairs medical centre; mean age: 54.9 years	Current opioid prescription and composite NMPOU risk measure	4	SUD [SCID]	Participants in the high prescription opioid misuse group had the highest rates of current substance use disorders (32% vs 20% and 0, P=0.009)
Morizio 2017, USA	Retrospective cohort study 2010-2015	923 patients admitted to a medical centre for heroin or non-heroin opioid overdose event; median age: 24	Lifetime history of NMPOU	2	History of prescription opioid abuse	History of NMPOU was more prevalent among those with non-heroin opioid overdose (46.9%), compared to the heroin overdose group (21.9%), P <0.0001
Reid 2002, USA	Retrospective 1997-1998	Medical records of 50 veteran affairs and 48 primary care centre patients; veteran affairs patients median age: 54 years; primary	Lifetime history of NMPOU based on patient records	2	Substance use	Prescription opioid abuse was disorder [medical associated with a lifetime history records review] of substance use disorder (AOR=3.8 [1.4-10.8])

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
		care centre patients median age: 55 years				
Romach 1999, Canada	Cross-sectional	339 long term codeine users recruited through newspaper adverts; mean age: 44 years	Past year codeine use	4	Dependence [DSM-IV]	Codeine dependence/abuse was present in 41% of long-term codeine users
Roux 2011, France	Prospective 1995-1996	235 HIV-infected opioid-dependent individuals; median age: 34 years	Injecting or sniffing PO in the previous 6 months	2	Withdrawal symptoms [self-report]	NMPOU was significantly associated with a reduced odds of experiencing opioid withdrawal symptoms (AOR=0.62 [0.36-0.89])
Saha 2016, USA	Cross-sectional 2012-2013	36,309 respondents in the NESARC-III	Past-year and lifetime NMPOU	4	Any other substance use disorders	NMPOU was significantly related to having any other substance use disorder (12-month AOR=2.95 [2.54-3.44]; lifetime AOR = 3.07 [2.67-3.53])
Schepis 2019, USA	Cross-sectional 2012-2013	14667 respondents in the NESARC-III	Persistent NMPOU (defined as past-year and prior)	4	Past-year substance use disorders	Persistent NMPOU significantly associated with higher past year prevalence of any substance use disorder (56.3% vs. 20.5%), alcohol use disorder (41.0% vs. 19.3%), and tobacco use disorder (48.4% vs. 24.6%) vs. no NMPOU
Schepis 2019, USA	Cross-sectional 2015-2016	114,043 respondents in the NSDUH	Past-year non-medical prescription fentanyl use	3	Past-year non-alcohol substance use disorders	Past-year non-medical prescription fentanyl use was associated with past-year non-alcohol substance use disorders (RR=20.64 [9.38-45.45]) compared to population controls
Schepis 2019, USA	Cross-sectional 2009-2014	103,920 adolescent respondents in in the NSDUH	Past 30 days NMPOU	4	Major depression in past year (DSM-IV)	NMPOU was significantly associated with major depression (AOR=1.91 [1.21-3.01])
Wu 2008, USA	Cross-sectional 2005-2006	2675 adolescent participants in the 2005-2006 NSDUH	Past year NMPOU	4	Dependence [DSM-IV]	Among adolescents age 12 to 17, weekly use of NMPO was significantly associated with dependence (AOR=5.45 [3.97-7.49])
Wu 2009, USA	Cross-sectional 2006	1290 adolescent participants in the 2006 NSDUH	Past year NMPOU	4	Dependence [DSM-IV]	Among adolescents age 12 to 17, 15.1% met DSM-IV criteria either for opioid abuse (7.4%) or dependence (7.7%) in the past year
Wu 2011, USA	Cross-sectional 2001-2002	2450 participants in the 2001-2002 National Institute on Alcohol Abuse and Alcoholism survey	Past year NMPOU	4	Substance use [DSM-IV]	Comparing prescription opioid disorder users *vs* users of non-opioid drugs, odds of any drug use disorder was increased among opioid users (AOR=1.31 [1.02-1.69])
F30 – F39: Mood [affective] disorders						
Ali 2015, USA	Cross-sectional 2008-2012	84,800 adolescents in the 2008-2012 NSDUH; mean age: 14.49 years	Lifetime NMPOU	4	Major depressive episode [Propensity scoring]	Adolescents who used prescription drugs non-medically were 33% to 35% more likely to experience major depressive episodes compared to their non-abusing counterparts ($P < 0.05$)
Barth 2013, USA	Case-control	Cases: 86 participants with current PO dependence; Controls:41 healthy participants in a larger study on stress; mean age: 35.4 years	Past 30 days NMPOU	4	Psychiatric disorders [ASI Lite]	Among individuals with prescription opioid dependence, prevalence of psychiatric disorders was: major depressive disorder 12.9%; panic disorder 20%; generalised anxiety disorder 14.1%

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Barth 2014, USA	Cross-sectional	307 individuals with non-alcoholic chronic pancreatitis ;mean age: 51 years	Past 30 days medication usage	4	Depressive symptoms [CESD]	A high opioid misuse measure score was associated with increased score on the depressive symptoms measurement scale (β = 0.38, *P*<0.0001)
Becker 2007, USA	Cross-sectional 2002-2004	6879 respondents in the NSDUH	Past year NMPOU	4	Depression [CIDI-SF]	Past-year non-medical use of prescription opioids was significantly associated with depressive symptoms [AOR=1.2 (1.01–1.5)]
Bohnert 2013, USA	Cross-sectional 2009	351 adults in a residential treatment program; mean age: 35.6 years	Past month NMPOU, Lifetime use	4	Depression [PHQ-9]	NMPOU was significantly associated with depression (AOR=1.06 [1.01-1.11], *P*=0.01)
Bouvier 2019, USA	Cross-sectional 2015-2016	199 young adults treatment program; mean age: 35.6 years	Past month NMPOU, Lifetime use	3	Diagnosed for depression	NMPOU use was significantly associated with a depressive disorder (AOR=1.51 [1.14-1.99], *P*<0.01)
Carrieri 2003, USA	Prospective 1995-2000	114 HIV-infected patients on buprenorphine maintenance treatment; mean age: 33.6 years	Buprenorphine injection misuse during the previous 6 months	2	Depression [CESD]	Depression was associated with injection misuse in the stabilised (ARR=1.04 [1.01-1.06]) and un-stabilised (ARR=1.05 [1.01-1.09]) phase of treatment
Edlund 2007, USA	Cross-sectional 1996-1997	9279 participants from a nationally representative study of the US civilian population	NMPOU in past 12 months	4	Depression	Depression was significantly [CIDI] associated with self-reported opioid misuse (OR = 2.23 [1.71-2.90], *P*< 0.001)
Edlund 2015, USA	Cross-sectional 2008-2012	112,600 adolescents aged 12–17, and 7100 adolescents aged 12–17	Past year NMPOU	4	MDE [NCS-A]	MDE was associated with NMPOU among all adolescents (OR = 1.51, *P*<0.001); in the sample of adolescents with NMPO use, 20% reported past year MDE
Fink 2015, USA	Cross-sectional 2011-2012	113655 participants in the 2011 and 2012 NSDUH	Past year NMPOU	4	MDE [DSM-IV]	Among adolescent and adult respondents, 5.8% and 4.5% reported any past-year NMPO respectively, while 8.6% and 6.8% met criteria for past-year MDE respectively
Grattan 2012, USA	Cross-sectional 2008-2009	1334 patients on chronic opioid therapy for non-cancer pain who had no history of substance abuse	NMPOU in past 2 weeks	4	Depression [PHQ-8 score]	Prescription opioid misuse was significantly associated with moderate depression (OR=1.75 [1.05-2.91, *P*=0.031]) and severe depression (OR=2.42 [1.46-4.02, *P*=0.001])
Green 2009, USA	Retrospective 2005-2008	29,906 respondent assessments from 220 treatment centres; mean age: 34.9 years	Past 30 days use of any prescription opioid	2	Depression [ASI-MV]	Prescription opioid abuse was associated with increased odds of depression in males (AOR=1.29 [1.09-1.53]) but not significant in females (AOR=1.15 [0.96-1.38])
Mackesy-Amiti 2015, USA	Cross-sectional 2008-2010	570 PWIDs recruited through street outreach and respondent driven sampling; mean age: 22.2 years	Past year and lifetime prescription opioid injection	4	Substance-induced major depression [DSM-IV]	Past year PO misuse was significantly associated with past year substance-induced major depression (AOR=1.81 [1.16–2.83])
Martel 2014, USA	Cross-sectional	82 patients with chronic pain being prescribed POs; mean age: 48.7 years	Past month NMPOU	4	Depression [self-report]	Depression (r = 0.25, *P*< 0.05) was significantly associated with prescription opioid misuse
Martins 2009, USA	Cross-sectional 2005-2006	8218 respondents in the NSDUH	Past year NMPOU	4	MDE [NCS-R and NCS-A]	Past year opioid users were significantly more likely to have past year MDE (AOR=1.4 [1.2-1.6]), compared to users of other illegal drugs

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Martins 2012, USA	Prospective 2001-2002; 2004-2005	34653 respondents in the NESARC	NMPOU over lifetime, past-year, or since last interview	2	Major depressive disorder [DSM-IV]	Baseline lifetime NMPOU was associated with incident major depressive disorder (AOR=1.4 [1.1-1.9])
Mason 2016, USA	Cross-sectional 2015	625 neurosurgery and orthopedic patients	NMPOU in the past 2 weeks	4	Depression [PROMIS]	Symptoms of depression symptoms experienced in the past week was significantly related to NMPOU in the past 2 weeks (AOR=1.16 [1.01-1.33])
Morasco 2008, USA	Randomised trial 2006-2007	127 patients recruited from a veteran's affairs medical centre; mean age: 59.8 years	Lifetime NMPOU	1	Depression [DSM-IV]	Participants reporting PO misuse were more likely to meet criteria for major depression (22% vs 3.7%, *P*=0.008)
Nugraheni 2020, USA	Cross-sectional 2016	40,632 respondents in the NSDUH	Past-year NMPOU	4	Major depressive episode	NMPOU associated with major depressive episode in past year (AOR=2.99 [2.47-3.62])
Price 2011, USA	Cross-sectional 2008-2009	351 patients seeking treatment from a drug and alcohol treatment program; mean age: 35.8 years	NMPOU in past 30 days	4	Depressive symptoms [PHQ]	Prescription opioid misuse was associated with greater depressive symptoms (AOR=1.09 [1.01-1.18])
Rigg 2015, USA	Cross-sectional 2010-2013	10201 respondents in the NSDUH; 18 years or older	Past-year NMPOU	4	Major depressive episode	NMPO users were not more likely to have experienced a major depressive episode in the past year compared to heroin users (AOR=0.774 [0.441-1.360] *P*-value=0.373)
Saha 2016, USA	Cross-sectional 2012-2013	36309 respondents in the NESARC-III	Past-year and lifetime NMPOU	4	Major depressive disorder	Past-year NMPOU was significantly related to having a major depressive disorder (AOR=1.26 [1.05-1.52]) and persistent depression (AOR=1.43 [1.06-1.92])
Sobieraj 2012, USA	Cross-sectional	1334 patients treated with chronic opioids	NMPOU in past 2 weeks	4	Depression [self-report]	Prescription opioid misuse was significantly associated with moderate depression (AOR=1.75 [1.05-2.91]) or severe depression (AOR=2.42 [1.46-4.02])
Tang 2016, China	Cross-sectional 2012	18686 Chinese high school students age 11-20; mean age: 15.43	Lifetime, past-year, and past-month NMPOU	4	Depressive symptoms [CES-D]	Depressive symptoms were more prevalent among participants reporting past-month NMPOU (16.6%) than non-users (8.8%); *P*-value <0.0001
Wheeler 2019, USA	Cross-sectional	208 African-American male prisoners	Lifetime NMPOU	4	Lifetime severe anxiety (ASI-V)	Lifetime NMPOU was associated with severe anxiety (AOR=3.97 [1.58-9.86])
Wu 2011, USA	Cross-sectional 2001-2002	2450 participants in the 2001-2002 National Institute on Alcohol Abuse and Alcoholism survey	Past year NMPOU	4	Mood disorder [DSM-IV]	Comparing prescription opioid users *vs* users of non-opioid drugs, odds of any mood disorder wasincreased among opioid users (AOR=1.07 [0.82-1.40]), though relationship was not statistically significant
Zale 2015, USA	Cross-sectional	24348 participants in the 2009 NSDUH	Past year NMPOU	4	Major depressive episode (MDE) [DSM-IV criteria]	Past year NMPOU was associated with past year MDE (AOR=2.44 [1.88-3.17], *P* <0.001)
F40 - F48: Neurotic, stress-related and somatoform disorders						
Becker 2007, USA	Cross-sectional 2002-2004	6879 respondents in the NSDUH	Past year NMPOU	4	Panic disorder, social phobia [CIDI-SF]	Past-year non-medical use of prescription opioids was significantly associated with panic symptoms [AOR=1.2 (1.04–1.5)], and phobic symptoms [AOR=1.2 (1.1–1.4)]

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Boyd 2014, USA	Cross-sectional 2009-2010	2627 secondary school students; mean age: 14.8 years	Lifetime NMPOU	4	Anxiety [YSR version of CBCL]	NMPOU associated with anxiety in 14.6% of sensation seekers and associated with anxiety in 3.3% of non-medical self-treaters
Feingold 2017, Israel	Cross-sectional	544 chronic pain patients	NMPOU use in past 30 days	4	Anxiety [GAD-7]	Patients who screened positive for anxiety were significantly more likely to screen positive for PO misuse than those without anxiety (AOR=2.18 [1.37-4.17])
Hall 2016, USA	Cross-sectional	406 victimised women on probation or parole; mean age: 37.2	Lifetime and past year NMPOU	4	Post-traumatic stress diagnostic scale	Participants who met diagnostic criteria for PTSD were more likely to report NMPOU (AOR=1.1 [0.61-1.8])
Kerridge 2015, USA	Cross-sectional 2012-2013	36309 noninstitutionalised adults residing in house-holds and selected group quarters	Lifetime and past year NMPOU	4	PTSD [DSM-5]	Past year NMPOU was associated with PTSD in men: (AOR=1.47 [1.04–2.09]), and women: (AOR=1.41 [1.05–1.91])
Mackesy-Amiti 2015, USA	Cross-sectional 2008-2010	570 PWIDs recruited through street outreach and respondent driven sampling; mean age: 22.2 years	Past year and lifetime prescription opioid injection	4	PTSD [DSM-IV]	Past year PO misuse was significantly associated with prior PTSD (AOR=2.45 [1.31–4.60])
Martel 2014, USA	Cross-sectional	82 patients with chronic pain being prescribed POs; mean age: 48.7 years	Past month NMPOU	4	Anxiety [self-report]	Anxiety (r =0.31, P<0.01) was significantly associated with prescription opioid misuse
Martins 2009, USA	Cross-sectional 2005-2006	8218 respondents in the NSDUH	Past year NMPOU	4	Anxiety [self-reported]	Past year opioid use was not significantly associated with past year anxiety disorder (AOR=1.2 [0.9-1.4])
Martins 2012, USA	Prospective 2001-2002; 2004-2005	34653 respondents in the NESARC	NMPOU over lifetime, past-year, or since last interview	2	Generalised anxiety disorder (GAD) [DSM-IV]	Baseline lifetime NMPOU was associated with incident GAD (AOR=1.5 [1.1-2.1])
Mason 2016, USA	Cross-sectional 2015	625 neurosurgery and orthopedic patients	NMPOU in the past 2 weeks	4	Anxiety	Symptoms of anxiety experienced symptoms in the past week were not [PROMIS] significantly related to NMPOU in the past 2 weeks (AOR=1.00 [0.89-1.11])
Saha 2016, USA	Cross-sectional 2012-2013	36309 respondents in the NESARC-III	Past-year and lifetime NMPOU	4	PTSD	NMPOU was significantly related to having PTSD (12-month AOR=1.41 [1.13-1.75]; lifetime AOR = 1.30 [1.11-1.51])
Smith 2016, USA	Cross-sectional 2004-2005	34653 respondents in the NESARC-III	Past-year and lifetime NMPOU	4	Past-year and lifetime PTSD diagnosis	Prevalence of a lifetime PTSD diagnosis was greater in those traumatic stress reporting NMPOU (19.8%) compared to non-users (9.3%). Prevalence of a past-year PTSD diagnosis was also greater in NMPO users (14.6%) compared to non-users (6.3%). Past-year PTSD diagnosis was associated with increased odds of past-year NMPOU (AOR=0.91, P<0.001)
Wu 2011, USA	Cross-sectional 2001-2002	2450 participants in the 2001-2002 National Institute on Alcohol Abuse and Alcoholism survey	Past year NMPOU	4	Anxiety [DSM-IV]	Comparing prescription opioid users vs users of non-opioid drugs, odds of any anxiety disorder was increased (AOR=1.28 [0.98-1.66]) though relationship was not statistically significant

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Xiao 2019, China	Cross-sectional 2015	159640 adolescents enrolled in the School-Based Chinese Adolescents Health Survey	Past year NMPOU	4	Past-year sleep disturbances	Past year NMPOU use associated past month sleep disturbances among boys (AOR=2.07 [1.66-2.58]) and girls (AOR=2.16 [1.68-2.77])
F00 – F99: Other psychiatric/mental health measures						
Back 2010, USA	Cross-sectional 2006	55,279 respondents in the NSDUH	Past year NMPOU	4	Psychological distress	NMPOU was significantly associated with having serious psychological stress in females (AOR: 1.65 [1.24-2.18]) but not significant in males (AOR=1.26 [0.85-1.85])
Becker 2011, USA	Retrospective 2006-2008	3238 respondents in the NSDUH	Past year NMPOU	2	Psychological distress [Kessler 6 inventory]	Serious psychological distress was present in 27.6% of participants
Boyd 2014, USA	Cross-sectional 2009-2010	2627 secondary school students; mean age: 14.8 years	Lifetime NMPOU	4	Conduct disorder	Nonmedical prescription opioid use was associated with conduct disorder in 46.3% of sensation seekers
Buttram 2014, USA	Clinical trial 2008-2010	515 MSM participating in a risk reduction intervention trial; mean age: 38.9 years	Past year and past 90 days injection NMPOU	2	Severe mental distress [GMDS]	Nonmedical prescription opioid use was associated with higher odds of severe mental distress (OR=1.72 [1.13-2.61]); P=0.011); severe mental distress prevalence: 57.9%
Chan 2020, USA	Cross-sectional 2016	11489 adolescent respondents in the NSDUH	Past year NMPOU	4	Past-year major depressive episode	Past year NMPOU was significantly associated with a past-year major depressive episode (AOR=1.60 [1.11-2.32])
Darke 1996, Australia	Cross-sectional	312 persons who inject drugs (PWID) recruited through street outreach; mean age: 28.8 years	Injection NMPOU in last 6 months	4	Psychological distress [GHQ score]	Methadone injectors had increased psychological distress (GHQ score: 10.2 vs. 7.8, P<0.05), and met diagnostic cut-off for psychopathology (67% vs 54%, P <0.05)
Fischer 2013, Canada	Cross-sectional 2010-2011	4023 adults and 3339 grade 7–12 public system students; students' mean age: 15.9 years; adults' mean age: 46.3 years	Past year NMPOU	4	Psychological distress [PHQ-2]	NMPOU was not significantly associated with increased odds of psychological distress among students (AOR=1.14 [0.76-1.70] nor among adults (AOR=1.63 [0.95-2.80]
Hruschak 2020, Australia	Cross-sectional 2014-2015	333 patients filling prescriptions at community pharmacies	Current NMPOU (Prescription Opioid Misuse Index)	4	Depression	Taking more medications than prescribed was significantly associated with depression (P<0.05)
Kozhimannil 2017, USA	Cross-sectional 2005-2014	8721 NSDUH respondents; women who were pregnant at the time of survey	Past-year, past-month NMPOU	4	Depression or anxiety	Among pregnant women, depression or anxiety in the past year was strongly associated with NMPOU in the past year (AOR=2.15 [1.52-3.04]). Past-year depression or anxiety was also associated with greater odds of past-month NMPOU (AOR=1.90 [1.10-3.30])
Kerridge 2015, USA	Cross-sectional 2012-2013	36,309 non-institutionalised adults residing in house-holds and selected group quarters	Lifetime to past year NMPOU	4	Personality disorders [DSM-5]	Past year NMPOU was associated with any personality disorder in men: (AOR=1.93 [1.52–2.45]), and women: (AOR=1.45 [1.13–1.86])
Mackesy-Amiti 2015, USA	Cross-sectional 2008-2010	570 PWIDs recruited through street outreach and respondent driven sampling; mean age: 22.2 years	Past year and lifetime prescription opioid injection	4	Antisocial personality disorder [DSM-IV]	Past year PO misuse was significantly associated with increased odds of antisocial personality disorder (AOR=2.15 [1.43–3.24])

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Martins 2007, USA	Cross-sectional 2002-2003	7810 respondents in the 2002-2003 NSDUH	Past year NMPOU	4	Mental health problems [CIDI]	Prescription opioid dependence was significantly associated with serious mental health problems (AOR=2.34 [2.04-2.69])
Martins 2015, USA	Cross-sectional 2008-2010	4421 respondents in the NSDUH	Past year NMPOU	4	Psychological distress [Kessler 6]	NMPOU was significantly associated with past-year serious psychological distress (AOR=2.09 [1.89–2.31])
Morizio 2017, USA	Retrospective cohort study 2010-2015	923 patients admitted to a medical centre for heroin or non-heroin opioid overdose event; median age: 24	Lifetime history of NMPOU	2	History of bipolar schizophrenia	History of bipolar schizophrenia was more prevalent among those with non-heroin opioid overdose (7.3%), compared to the heroin overdose group (2.5%), *P* <0.0014
Novak 2016, Denmark, Germany, Great Britain, Sweden	Cross-sectional 2014	22,070 survey respondents in the European Union ages 12-49	Lifetime and past year NMPOU	4	Serious psychological distress [K9]	NMPO users were more likely to report non-specific psychological distress (AOR=3.2 [2.6-3.9])
Ouellet 2012, USA	Cross-sectional 2002-2005	645 non-injecting heroin users recruited through street outreach and respondent driven methods	Lifetime history of NMPOU	4	Psychiatric disorder [self-reported]	Being diagnosed with a psychiatric disorder was associated with PO use prior to heroin initiation (AOR=2.2 [1.2-4.1)
Rigg 2015, USA	Cross-sectional 2010-2013	10,201 respondents in the NSDUH;18 years or older	Past-year NMPOU	4	Psychological distress	NMPO users were not more likely to have experienced psychological distress in the past year compared to heroin users (AOR=0.876 [0.537-1.428] *P*-value=0.596)
Romach 1999, Canada	Cross-sectional	339 long term codeine users recruited through newspaper adverts; mean age: 44 years	Past year codeine use	4	Psychological problems [self-reported]	A fraction of the subjects identified depression (13%) and worry (12%) as psychological consequences of long term codeine use
Saha 2016, USA	Cross-sectional 2012-2013	36309 respondents in the NESARC-III	Past-year and lifetime NMPOU	4	Any personality disorder	NMPOU was significantly related to having any personality disorder (12-month AOR=1.70 [1.45-1.99]; lifetime AOR = 1.97 [1.75-2.22])
Shield 2011, Canada	Cross-sectional 2008-2009	2030 participants in the 2008-2009 Center for Addiction and Mental Health monitor	NMPOU in past 12 months	4	Psychological distress [GHQ-12]	NMPOU was associated with increased odds of psychological distress in men (AOR=7.55 [2.87-19.88]) and women (AOR=4.21, 1.61-11.00])
Sproule 1999, Canada	Cross-sectional	399 regular users of codeine recruited through newspaper adverts; mean age: 43.5 years	Past year NMPOU	4	Mental health problems [self-report]	Significantly more subjects that were codeine dependent had sought help for a mental health problem (*P* <0.001)
Subramaniam 2009, USA	Cross-sectional	94 adolescents (ages 14-17 years) with past year diagnosis of opioid use disorder; mean age:16.9 years	NMPOU in past 30 days	4	Psychiatric disorders [DICA-IV]	Prescription opioid users presented with higher rates of current ADHD (*P*=0.01) and manic episodes (*P*=0.04)
Tetrault 2007, USA	Cross-sectional 2003	55,230 participants in the 2003 NSDUH	Past year NMPOU	4	Serious mental illness [Kessler inventory]	Past year NMPOU was significantly associated with increased odds of serious mental illness in females (AOR=1.67 [1.29-2.17]) but not significantly associated with increased odds in males (AOR=1.25 [0.91-1.70])
Tragesser 2013, USA	Cross-sectional	606 students aged 18 to 52 taking psychology courses; mean age: 20.4 years	NMPOU in past 3 months	4	Borderline personality disorder [PAI-BOR]	Opioid misuse and dependence features were positively associated with heightened levels of borderline personality disorder features (*P* <0.001)

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Uosukainen 2014, Finland	Cross-sectional 2001-2008	1227 clients seeking treatment for buprenorphine and amphetamine abuse; mean age: buprenorphine users 25.8 years, amphetamine users 27.6 years	Current and lifetime NMPOU	4	Psychotic symptoms [self-reported]	Buprenorphine abuse was associated with reduced odds of psychotic symptoms (AOR=0.33, [0.24-0.45], P <0.001)
Vietri 2014, USA	Cross-sectional 2010, 2011	25,864 participants in the 2010 and 2011 US National Health and Wellness Survey	NMPOU in the 3 months prior to the survey (modes of use: chewing, smoking, snorting, rectal, injecting)	4	Psychiatric conditions [self-reported]	PO abuse was significantly associated with self-reported psychiatric conditions (AOR=1.71 [1.28-2.27], P=0.0002)
Wang 2013, USA	Cross-sectional 2008-2009	75,964 participants in the 2008-2009 NSDUH	Past year NMPOU	4	Psychological distress [K6 scale]	Non-medical use of prescription opioids was associated with increased odds of psychological distress in urban (AOR=1.64 [1.41–1.89]) and rural residents (AOR=1.63 [1.23–2.17])
Wasan 2007, USA	Prospective	288 patients prescribed opioids for chronic pain; mean age: 50.5 years	Current NMPOU	2	Psychiatric morbidity [PDUQ]	Presence of psychiatric morbidities such as mood disorders, psycho-social stressors, and psychologic problems was associated with self-reported measures of prescription opioid misuse (COMM P <0.01, SOAPP P <0.05)
XI. Diseases of skin and subcutaneous tissue **L00 – L99: Infections of the skin and subcutaneous tissue**						
Ambekar 2015, India	Cross-sectional	902 male PWID recruited from harm reduction centres; mean age: 33.4 years	Injection PO use in past 3 months	4	Abscess, blocked veins [self-reported]	Prescription opioid injectors were significantly more likely to develop abscess or blocked veins ever in their injecting life (Abscess: RR=1.39 [1.05-1.85]; blocked veins: RR=2.513 [1.89-3.35])
Darke 1996, Australia	Cross-sectional	312 PWID recruited through street outreach; mean age: 28.8 years	Injection PO use in last 6 months	4	Thrombosis, abscess [self-reported]	Methadone injection was associated with abscesses and infections (OR=2.4 [1.3-4.4]), and thrombosis (OR=2.2 [1.1-4.6]); prevalence of abscesses and infections: 23%; prevalence of thrombosis: 16%
Degenhardt 2006, Australia	Cross-sectional 2001-2004	795 PWID recruited through street outreach; mean age: 33.8 years	Injection PO use in last 6 months	4	Injection site harms (difficulty finding veins, bruising/scarring) [self-reported]	After covariate adjustment, recent morphine injection was not significantly associated with injection site harms; prevalence of difficulty finding veins was 36%, prevalence of scarring or bruising was 27%
Jenkinson 2005, Australia	Cross-sectional 2002	156 respondents in the Melbourne arm of the Illicit Drug Reporting System; mean age: 30 years	Injection PO use in last 6 months	4	Injection-related health problems (overdose, bruising abscesses, scarring, thrombosis) [self-reported]	Buprenorphine injection was not significantly associated with increased odds of injection-related health problems (AOR=2.9 [0.98-8.8])
XVI. Certain conditions originating in the perinatal period **P05-P08: Disorders related to length of gestation and fetal growth**						

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Almario 2009, USA	Retrospective 2000-2006	258 opiate-addicted women treated with methadone; mean age of mothers with preterm delivery: 28.7 years	Current NMPOU	2	Preterm delivery	NMPOU in mothers treated for addiction was not significantly associated with lower odds of preterm birth (AOR=0.9 [0.4-2.2])
Liu 2010, Australia	Retrospective 2000-2006	215 opioid dependent mothers; median age: 27.2 years	Current NMPOU	2	IUGR [ICD-10-AM]	Risk of IUGR is higher in non-smoking opioid dependent mothers compared to non-smoking non-opioid dependent mothers (RR=3.48 [1.70-7.14])
Maeda 2014, USA	Retrospective 1998-2011	113,105 hospitalisations for delivery identified in the nationwide inpatient sample		2	Stillbirth, IUGR preterm labor, [ICD-9-CM]	Maternal opioid abuse or dependence was associated with stillbirth (AOR=1.5 [1.3-1.8]), preterm labor (AOR=2.1 [2.0-2.3]), IUGR (AOR=2.7 [2.4-2.9]), maternal death during hospitalisation (AOR=4.6 [1.8-12.1])
P90 – P96: Other disorders originating in the perinatal period						
Kelly 2011, Canada	Retrospective 2009-2010	482 live births that occurred at a Canadian health centre; mean age: 24.5 years	Oral use, snorting or injection of opioids (most commonly oxycodone)	2	NAS [Infant Finnegan scores]	Narcotic-exposed neonates experienced NAS 29.5% of the time; daily maternal use was associated with a higher rate of NAS (66.0%)
Lee 2015, USA	Retrospective 2007-2013	139 cases of NAS pooled from a large Medicaid health plan	In utero exposure to prescription opioids	2	NAS [ICD-9], hospital length of stay	In utero exposure to methadone or buprenorphine leads to an average NICU length of stay of 21 days for NAS treatment
McQueen 2015, Canada	Retrospective 2010-2011	131 infant/mother pairs with NAS symptoms and maternal substance abuse; mean age of mothers at delivery: 25.6 years	In utero exposure to prescription opioids	2	NICU admission; NAS [MFS tool]	Among the eligible sample of infants, 78.6% were admitted to the NICU and 72.5 % of eligible sample received pharmacologic treatment for NAS
XVIII. Symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified R40-R46. Symptoms and signs involving cognition, perception, emotional state and behaviour						
Ashrafioun 2017, USA	Cross-sectional 2014	24,653 respondents in the NSDUG	Past-year NMPOU	4	Suicidal ideation [self-reported]	Past-year suicidal ideation was significantly associated with less than monthly (AOR=1.52 [1.21-1.91]), monthly to weekly (AOR=1.41 [1.04-1.93]), and weekly or more (AOR=1.62 [1.19-2.21]) NMPOU in the past year
Barman-Adhikari 2019, USA	Cross-sectional 2016-2017	1426 young adults experiencing homelessness	Past-month NMPOU	4	Lifetime suicidal ideation	Past-month NMPOU was associated with lifetime suicidal ideation (AOR=1.8 [1.1-3.0])
Bohnert 2013, USA	Cross-sectional 2009	351 adults in a residential treatment program; mean age: 35.6 years	Past month NMPOU Lifetime use	4	Suicidal ideation [BSS]	Non-medical PO use was not significantly associated with suicidal ideation (AOR=1.01 [0.95-1.07])
Epstein-Ngo 2014, USA	Prospective	575 patients in an urban emergency department who screened positive for past 6 months drug use; mean age: 20 years	NMPOU in past 6 months	2	Aggression [TLFB-AM]	Prescription opioid misuse was more likely immediately prior to dating violence than non-dating violence (AOR=6.24 [2.81-13.88])

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Fischer 2013, Canada	Cross-sectional 2010-2011	4023 adults and 3339 grade 7–12 public system students; students' mean age: 15.9 years; adults' mean age: 46.3 years	Past year NMPOU	4	Suicidal ideation [self-reported]	Among students, NMPOU was significantly associated with suicidal ideation (AOR=2.13, [1.12-4.06])
Guo 2016, China	Prospective longitudinal 2009-2010, 2011-2012	3273 adolescent students; mean age: 13.7	Past-year NMPOU	1	Suicidal ideation	Baseline NMPOU was associated with suicidal ideation at one year follow-up (AOR=2.31 [1.30-4.11])
Han 2017, USA	Cross-sectional 2015	51,200 respondents in the 2015 NSDUH identified as prescription opioid users	Lifetime and past-year NMPOU	4	Suicidal ideation	Among adults with prescription opioid misuse, prevalence of past-year suicidal ideation was 21.5% (95% CI 18.77-24.46)
Havens 2011, USA	Cross-sectional 2001-2004	800 felony probationers recruited into a HIV-prevention trial; median age: 32.3 years	Lifetime PO injection	4	Risky behaviour [self-reported] [reported]	Participants indicating lifetime injection of POs were 14.7 times more likely to have reported participating in risky injection behaviours (AOR=14.7 [7.7-28.1])
Humeniuk 2003, Australia	Cross-sectional 1996-1997	365 heroin users recruited through snowball sampling; mean age: 28.9 years	Injection PO use in last 6 months	4	Risky behaviour [self-reported]	Methadone injectors were significantly more likely to use other drug types intravenously than non-injectors of methadone, both on a life-time scale (F=48.0, df=1, 362, P=0.000) and over the last 6 months (F=15.4, df=1, 362, P=0.000)
Kuramoto 2011, USA	Cross-sectional 2009	37,933 respondents in the NSDUH	Lifetime and past year NMPOU	4	Suicidal ideation [self-reported]	NMPOU was significantly associated with suicidal ideation (AOR=1.88 ([1.13-3.12])
Lin 2015, USA	Cross-sectional	1076 youths ages 12–18, presenting to primary care community health clinics in two urban settings	NMPOU in past 3 months	4	Delinquency [self-reported]	NMPOU was significantly associated with non-violent delinquency (OR=1.06 [1.01-1.12])
Rigg 2019, USA	Cross-sectional 2012-2016	22,693 respondents in the NSDUH	Past year NMPOU	4	Suicide planning and attempts	No significant differences in suicidality between participants who engage in NMPOU use in urban (AOR=1.20 [0.67-2.13]) and rural settings (AOR=2.12 [0.43-10.55])
Schepis 2019, USA	Cross-sectional	17,608 adult respondents in the NSDUH	Past-year NMPOU	4	Suicidal ideation	NMPOU was significantly associated with suicidal ideation (AOR=1.84 [1.07-3.19])
Tang 2016, China	Cross-sectional 2012	18,686 Chinese high school students age 11-20; mean age: 15.43	Lifetime, past-year, and past-month NMPOU	4	Suicidal ideation	Suicidal ideation was more prevalent among participants reporting past-month NMPOU (34.9%) than non-users (21.2%); P-value <0.0001
Wilkins 2021, USA	Cross-sectional 2019	13,667 high school students enrolled in the Youth Risk Behavior Survey	Current NMPOU	4	Past-year suicidal ideation, planning and attempts	Current NMPOU significantly associated with higher prevalence ratios for suicidal ideation (APR=2.30 [1.97-2.69]), planning (APR=2.33 [1.99-2.79]) and attempts (APR=3.21 [2.56-4.02])
Young 2012, USA	Cross-sectional 2009-2010	2597 middle and high school students enrolled in two school districts, mean age: 14.8 years	NMPOU in past 12 months	4	Aggressive behaviour [YSR version of CBCL]	Sensation seeking non-medical use of prescription opioids was associated with rule breaking behaviour, high risk of substance dependence, and aggressive behaviour
R50-R69: General symptoms and signs						

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Becker 2007, USA	Cross-sectional 2002-2004	6879 respondents in the NSDUH	Past year NMPOU	4	General health status [self-reported]	Respondents meeting criteria for abuse/dependence were more likely to self-report fair/poor health (AOR 2.1 [1.4–3.0])
Black 2013, USA	Cross sectional 2007-2011	29,459 PO users recruited from 540 treatment facilities; mean age=33.1 years	Past 30 days NMPOU	4	General health status (liver disease, ER visit) [ASI-MV criteria]	Prescription opioid injection was significantly associated with liver disease (OR=1.71 [1.53-1.90], $P < 0.0001$]) and visit to the ER in the past 30 days (OR=1.84 [1.71-1.98], $P < 0.0001$).
Brunet 2015, Canada	Cross-sectional 2013	1238 HIV/HCV co-infected persons [800 in prevalence cohort, 582 in incidence cohort]	Injection PO use in past 6 months	4	General health status (liver fibrosis progression) [APRI score]	Prescription opioid injection was associated with faster progression to liver fibrosis [hazard odds ratio=1.20 (0.73-1.67)] though the association was not statistically significant
Catalano 2011, USA	Prospective	912 students from 1st or 2nd grade to age 21; mean age: 16.2 years	Past year and lifetime NMPOU	2	General physical [self-reported] and mental health consequences [CIDI]	Ever use of NMPO was associated with a 7.9 greater odds of having a current drug use disorder, 2.1 greater odds of a mood disorder, 1.4 greater odds of poor/fair health, 2.6 greater odds of being violent
Choo 2014, USA	Retrospective 2011	426,010 DAWN-defined visits involving prescription opioid	NMPOU at emergency department presentation	2	ED presentation	Use of prescription opioids was associated with decreased odds of hospital admission in females (AOR=0.65 [0.54–0.77]) and males (AOR=0.62 [0.46–0.83])
Fischer 2013, Canada	Cross-sectional 2010-2011	4023 adults and 3339 grade 7–12 public system students; students' mean age: 15.9 years; adults' mean age: 46.3 years	Past year NMPOU	4	Physical health [self-reported]	NMPOU was not significantly associated with self-reported poor/fair health among students (AOR=1.30 [0.69-2.46] nor among adults (AOR=1.41 [0.79-2.52])
Green 2009, USA	Retrospective 2005-2008	29,906 respondent assessments from 220 treatment centres; mean age: 34.9 years	Past 30 day NMPOU	2	>5 ER visits in past 30 days [self-reported]	Prescription opioid abuse was associated with marginally increased odds of ER visits in males (AOR=1.06 [0.56-2.03]) and in females (AOR=1.75 [0.97-3.14]), though the associations were not statistically significant
Griffin 2015, USA	Clinical trial	653 prescription opioid dependent patients; mean age: 33.2 years	Current NMPOU dependence	2	Health-related quality of life [SF-36]	Prescription opioid-dependent patients had worse physical and mental quality of life than a healthy population or a general population [mental scores=15.3 points vs healthy population and 12.3 points vs general population; physical scores=7.1points vs healthy population and 1.7 points vs general population]
Han 2017, USA	Cross-sectional 2015	51,200 respondents in the 2015 NSDUH identified as prescription	Lifetime and past-year NMPOU	4	Hypertension	Among adults with prescription opioid misuse, prevalence of hypertension was 6.0% (95% CI, 5.06-7.03)
Hartwell 2014, USA	Case-control	68 non-treatment seeking individuals recruited through advertisements (33 PO dependent cases and 35 healthy controls)	NMPOU in the one month prior to baseline visit	3	Sleep quality [PSQI and ISI]	Poor sleep quality was identified in 80.6% of the PO dependent group, as compared to 8.8% of the control group ($P<0.001$)
Jeevanjee 2014, USA	Cross-sectional 2007-2008	258 HIV positive individuals recruited from homeless shelters, free meal programs, and single	NMPOU use in past 90 days	4	Treatment adherence [self-reported]	PO misuse was significantly associated with an increased odds of incomplete adherence to treatment (AOR=1.47 [1.06-2.03])

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
		room occupancy hotels; mean age: 48 years				
Mason 2016, USA	Cross-sectional 2015	625 neurosurgery and orthopedic patients	NMPOU in the past 2 weeks	4	Pain and depression [PROMIS]	Interaction between pain and depression experienced in the past week was significantly associated with NMPOU (AOR=0.96, [0.92-0.99])
McCabe 2013, USA	Prospective 2009-2011	2050 middle and high school students from two public school districts	Past year NMPOU	1	Physical pain [YSR], pain [YSR]	NMPOU was not significantly associated with increased odds of physical pain in the previous 6 months during year 2 of study [OR=2.0, 0.7-5.6]
Morizio 2017, USA	Retrospective cohort study 2010-2015	923 patients admitted to a medical centre for heroin or non-heroin opioid overdose event; median age: 24	Lifetime history of NMPOU	2	Hospital admission due to overdose	84.6% of patients in the non-heroin opioid overdose group required hospital admission due to overdose compared to 72.2% of the heroin overdose group, $P<0.0001$
Nielsen 2013, Australia	Cross-sectional 2011	141 participants recruited from opioid substitution treatment programs; mean age: 40.8 years	NMPOU in past 28 days	4	Pain [Brief Pain Inventory]	Any illicit PO use was associated with pain (OR=1.85 [0.78-4.39], though the association was not statistically significant
Patra 2009, Canada	Prospective 2004-2005	582 participants from the most recent follow-up in the OPICAN study; mean age: 35.2 years	NMPOU in past 30 days (non-injecting)	4	Personal health status [self-reported]	Among participants who majorly use prescription opioids, 55% reported poor or fair health status in past 30 days
Price 2011, USA	Cross-sectional 2008-2009	351 patients seeking treatment from a drug and alcohol treatment program; mean age:35.8 years	NMPOU in past 30 days	4	Physical functioning [SF-12]	Prescription opioid misuse was associated with lower physical functioning; as physical functioning increased (AOR=0.94 [0.91-0.98]), likelihood of NMPOU decreased
Schepis 2014, USA	Prospective 2001-2002, 2004-2005	34,653 participants in the NESARC	Lifetime NMPOU	2	Health related quality of life [SF-12]	NMPOU initiation was generally associated with poorest longitudinal outcomes for health related quality of life
Stein 2015, USA	Cross-sectional 2012-2013	328 primary care patients treated with buprenorphine; mean age: 38.7 years	NMPOU use in previous month	4	Pain [Brief Pain Inventory]	NMPOU was associated with moderate/severe chronic pain (OR=1.55 [0.29-8.23]), though the association was not statistically significant
Tang 2016, China	Cross-sectional 2012	18,686 Chinese high school students age 11-20; mean age: 15.43	Lifetime, past-year, and past-month NMPOU	4	Poor sleep [CPSQI]	Past-year and lifetime NMPOU was significantly associated with poor sleep among participants (AOR=1.47 [1.17-1.85]; AOR=1.43 [1.28-1.60])
Tetrault 2007, USA	Cross-sectional 2003	55,230 participants in the 2003 NSDUH	Past year NMPOU	4	>5 ER visits in past 1 year [self-reported]	Past year NMPOU was not significantly associated with increased odds of ER visits in females (AOR=1.77 [0.98-3.21]) nor reduced odds in males (AOR=0.74 [0.31-1.78])
Vietri 2014, USA	Cross-sectional 2010, 2011	25864 participants in the 2010 and 2011 US National Health and Wellness Survey	NMPOU in the 3 months prior to the survey (modes of use: chewing, smoking, snorting, rectal, injecting)	4	Work productivity and general health [WPAI:GH]	PO tampering and abuse was associated with greater loss of productivity and increased use of health care ($P<0.05$)

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
XIX. Injury, poisoning and certain other consequences of external causes T36 – T50: Poisoning by drugs, medicaments and biological substances						
Alexander 2004, USA	Retrospective 1997-2002	1,175,781 opioid-related emergency medical services patient encounters; mean age=35.4 year	Current NMPOU at patient encounter	2	Non-fatal overdose	Patients diagnosed as having poisoning or overdose increased by 47% over the study period
Black 2013, USA	Cross sectional 2007-2011	29,459 PO users recruited from 540 treatment facilities; mean age=33.1 years	Past 30 days NMPOU (oral route:90%; snorting:36%; injection:32%)	4	Non-fatal overdose	Prescription opioid injection was significantly associated with non-fatal overdose (OR: 1.32 [1.22-1.42], P<0.0001)
Bohnert 2013, USA	Cross-sectional 2009	351 adults in a residential treatment program; mean age: 35.6 years	Past month NMPOU, Lifetime use	4	Overdose, Addiction Severity Index, ASI]	Non-medical PO use was associated with past history of overdose (AOR=2.10 [1.10-4.02], P=0.03)
Bonar 2014, USA	Cross sectional 2008-2009	326 patients recruited from substance use disorder treatment centres; mean age: 35.1 years	Past 30 days NMPOU	4	Overdose	Past 30 days heavy NMPOU was associated with lifetime overdose (OR=2.99 [1.53-5.84])
Brands 2004, Canada	Retrospective 1997-1999	178 new admission patients in a methadone maintenance treatment program; mean age: 34.5 years	Current PO injection	2	Overdose	Among those who inject prescription opioids-only, 46.5% reported ever overdosing on opioids
Bretteville-Jensen 2015, Norway	Cross sectional 2006-2013	1355 street-recruited PWID; mean age: 37 years	PO injection in past 4 weeks	4	Non-fatal overdose	Illicit use of buprenorphine was associated with an increased risk of non-fatal overdose, [OR=1.132, S.E=0.298]
Calcaterra 2013, USA	Retrospective 1999-2009	All overdose deaths in the US among 15–64 year olds from 1999 to 2009	Death certificate mention of PO	2	Fatal overdose	Age adjusted death rate related to pharmaceutical opioids increased almost 4-fold from 1999 to 2009 (1.54/100,000 p-y [95% CI 1.49-1.60] to 6.05/100,000 p-y [95% CI 5.95-6.16; P<0.001)
CDC 2011, USA	Retrospective 1999-2008	36,450 deaths that were attributed to drug overdose	Death certificate mention of PO	2	Fatal overdose	Opioid pain relievers were involved in 14,800 deaths (73.8%) of the 20,044 prescription drug overdose deaths
CDC 2013, USA	Retrospective 1999-2010	15,323 deaths among women that were attributed to drug overdose	Death certificate mention of PO	2	Fatal overdose	Deaths from opioid pain relievers increased fivefold for women and 3.6 times for men between 1999 and 2010
CDC 2000, USA	Retrospective 1996-1999 data	484 decedents where heroin or opiate intoxication was listed as a cause of death; median age: 40 years	Death certificate mention of PO	2	Fatal overdose	Opiate overdose death rate increased from 3.1 per 100,000 population in 1990 to 6.6 in 1999, an increase of 112.9% (P<0.001)
Challoner 1990, Canada	Retrospective 1977-1987	57 cases of overdose on pentazocine; median age: 28 years	Recent ingestion of pentazocine	2	Overdose	Reasons for overdose were attempted suicide (35 cases) excessive therapeutic use (11 cases) and drug abuse to obtain a “high” (11 cases)
Cheng 2020, Canada	Cross-sectional 2013-2016	599 people who report opioid use in past 6 months	Past six month NMPOU	3	Non-fatal overdose in past six months	No significant differences in non-fatal overdose risk among those who did and did not acquire opioids from physicians

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Clayton 2019, USA	Cross-sectional 2017	14756 respondents in the Youth Risk Behavior Survey (Grades 9-12)	Lifetime NMPOU	2	Past-year suicide planning and attempt	NMPOU associated with past-year suicide planning (AOR=2.41 [2.15-2.71]) and attempt (AOR=3.45, [2.86-4.17])
Clayton 2019, USA	Cross-sectional 2017	3697 respondents in the Virginia Youth Survey (Grades 9-12)	Past-year and current NMPOU	4	Past-year suicide planning and attempt	Current NMPOU associated with past year suicide attempt (APR=2.18 [1.21-3.93])
Darke 1996, Australia	Cross-sectional	312 PWID recruited through street outreach; mean age: 28.8 years	Injection PO use in last 6 months	4	Overdose [self-reported]	Ever injecting methadone was associated with overdose (OR=2.2 [1.4-3.5]); also injectors of methadone in previous 6 months were more likely to overdose (OR=2.5 [1.4-4.6])
Darke 2002, Australia	Cross sectional 1996-2000	788 PWID interviewed in Sydney; mean age: 28.6 years	Injection PO use in previous 6 months	4	Overdose	Among the methadone injectors, 72% had ever overdosed
Degenhardt 2009, Australia	Retrospective 1985-2006	42,676 people who entered opioid pharmacotherapy program	PO dispensations from the New South Wales Pharmaceutical Drugs of Addiction System linked to overdose events	2	Overdose	Drug overdose and trauma were the major contributors of death
Dhalla 2011, Canada	Cross sectional 2006	Family physician of participants who were eligible for prescription drug coverage; other details from office of the chief coroner	Administrative prescription data on PO dispensation	4	Mortality related to opioid use	The number of opioid-related deaths increased across prescribing-volume quintiles (P<0.001)
Fernandes 2015, USA	Retrospective 2003-2012	358 Montana residents aged 18–64 years who died from unintentional PO poisoning	PO enrolment via Medicaid	2	Overdose	Age-adjusted mortality rate per 100,000 from opioid poisoning in Montana Medicaid adults was eight times higher than the rate for non-Medicaid Montana adults (38.2 [CI (30.7–45.7]) vs. 4.7 (CI (4.1–5.3)])
Fischer 2004, Canada	Cross sectional 2002	651 illicit opioid users recruited from 5 Canadian cities; mean age: 34.8 years	Injection PO use in past 30 days	4	Overdose	Non-injection administration of hydromorphone in the past 30 days was a predictor of overdose episodes (OR=2.73 [1.37–5.46])
Fischer 2008, Canada, USA	Cross-sectional 2004-2005	448 participants of which 304 (62.8%) were classified as prescription only users	Injection PO use in past 30 days	4	Overdose [self-reported], Emergency room use [self-reported]	PO use was associated with lower odds of ER use (OR=0.88, [0.41-1.87]) and associated with increased odds of overdose (OR=1.16 [0.32-4.18]), though the associations were not statistically significant
Green 2011, USA	Retrospective 1997-2007	2900 adult with accidental/ undetermined drug intoxication deaths	Post mortem toxicology report of NMPOU	2	Fatal overdose	From 2001, intoxication deaths involving any prescription opioid increased from previous years, (linearly: 25.14, P<0.001)
Hakkinen 2010, Finland	Retrospective 2000-2008	12,891 subjects on which a post mortem toxicological analyses was performed	Post mortem toxicology report of NMPOU	2	Fatal overdose	Proportion of fatal prescription opioid poisonings out of all fatal drug poisonings increased from 9.5% (52 cases) in 2000 to 32.4% (179 cases) in 2008, being 22.3% over the whole period
Hall 2008, USA	Cross sectional 2006	295 residents who died of unintentional pharmaceutical overdoses; mean age: 39 years	Post mortem toxicology report of NMPOU	4	Fatal overdose [post mortem records]	Pharmaceutical diversion was associated with 186 (63.1%) deaths, while 63 (21.4%) were accompanied by evidence of doctor shopping

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Han 2015, USA	Retrospective 2003-2013	472,200 persons aged 18 through 64 years who participated in the 2003-2013 NSDUH. Mortality data from 2003-2013 National Vital Statistics System's Multiple Cause of Death Files	NMPOU in past 12 months	2	Fatal overdose	Among adults aged 18 through 64 years, overdose death rates involving prescription opioids increased from 4.5 per 100 000 (CI 4.42-4.61) in 2003, to 7.8 per 100 000 (CI:7.64-7.89) in 2013 (absolute difference: 3.3; [CI: 3.09-3.41])
Hardt 2013, USA	Retrospective 1999-2005	169 drug-positive, pregnancy-associated non-natural deaths		2	Mortality related to opioid use	At least one prescription drug was found in 91 of the 169 cases (54%) of drug-positive, pregnancy-associated non-natural deaths
Hassanian-Moghaddam 2013, Iran	Retrospective 2009-2010	525 patients referred with pure tramadol intoxication		2	Non-fatal overdose	The mean dose ingested by patients experiencing apnea was 2125 ± 1360 mg (range, 200-4600 mg) with 359 (68.4%) engaged in deliberate self-poisoning
Havens 2011, USA	Cross sectional	400 rural drug users median age: 31 years	Past 30-day PO injection	4	Non-fatal overdose	Rural drug users with history of overdose were more likely to have injected with prescription opioids
Iversen 2017, Australia	Cross-sectional 2014	1488 Australian NSP survey respondents	PO injection in past 6 months	4	Non-fatal overdose [self-reported]	PO injection in the previous 6 months was associated with non-fatal overdose in the past year (AOR=1.81 [1.36-2.42])
Jenkins 2011, USA	Cross sectional 2009	443 participants at syringe exchanges; median age: 38 years	PO injection in past 4 months	4	Non-fatal overdose	Injection of prescription type opioid was not significantly associated with increased odds of non-fatal overdose (OR=1.84 [0.70–4.80])
Kerr 2007, Canada	Prospective 1996-2004	1587 injection drug users median age: 33.4 years	PO injection in previous 6 months	2	Non-fatal overdose	Non-fatal overdose was significantly associated with non-injection opiate use (AOR=1.16 [1.03-1.3], p=0.014) but not significantly associated with morphine injection (AOR=1.01 [0.84-1.22], *P*=0.878)
Lake 2015, Canada	Prospective 2005-2013	1614 adult illicit drug users recruited through self-referral and street outreach; median age: 41.6 years	PO injection in previous 6 months	1	Non-fatal overdose	Prescription opioid use was independently associated with non-fatal overdose (AOR: 1.61 [1.32–1.95])
Lake 2015, Canada	Prospective 2005-2014	1660 adult illicit drug users recruited through self-referral and street outreach; median age: 41.1 years	PO injection in previous 6 months	2	Non-fatal overdose	Exclusive prescription opioid injection was not significantly associated with increased odds of non-fatal overdose (AOR:1.17 [0.74–1.86])
Lanier 2012, USA	Case-control 2008-2009	Cases: 278 decedents who met the study criteria, Controls: 1308 Utah BRFSS respondents; median age: 41 years	Past year NMPOU	3	Mortality related to opioid use	Oxycodone was the most frequent opioid cause of death among cases, while hydrocodone was the most frequently reported opioid among comparison group
Madadi 2013, Canada	Retrospective 2006-2008	2330 drug-related deaths history retrieved from the Office of the Chief Coroner; median age: 44 years	Mention of POs in Coroner's reports	2	Mortality related to opioid use	Oxycodone was involved in approximately one-third of opioid-related deaths (35%)
Maloney 2009, Australia	Retrospective case-control 2004-2008	1500 opioid-dependent individuals; mean age: males 37.2 years, females 35.3 years	Lifetime NMPOU	2	Non-fatal overdose	Ever injecting opioids was associated with non-fatal overdose [OR: 11.90 (4.18–33.33)] and 37% reported non-fatal overdose

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Morizio 2017, USA	Retrospective cohort study 2010-2015	923 patients admitted to a medical centre for heroin or non-heroin opioid overdose event; median age: 24	Lifetime history of NMPOU	2	Fatal overdose	4.2% of patients who experienced non-heroin opioid overdose event had a discharge status of 'died', compared to 4.5% of the heroin overdose group, *P* >0.0001
Pabayo 2013, Canada	Prospective	1931 PWID recruited via self-referral, word of mouth and street outreach	PO injection in past 30 days	2	Non-fatal overdose	Morphine injection was associated with non-fatal overdose experience during follow-up (OR = 1.81 [1.24-2.64])
Roux 2008, France	Prospective 2004, 2005	111 stabilised patients receiving office-based buprenorphine; median age: 38 years	Injection PO use in last 30 days	2	Overdose [self-reported]	PO injection was significantly associated with experiencing overdose (OR=2.4 [1.1-5.3], *P*=0.04)
Roxburgh 2017, Australia	Retrospective cohort study 2007-2014	8382 clients of a medically supervised injecting centre	On-site PO injection	2	Non-fatal overdose	Rate of oxycodone overdose was 3.1 times (95% CI, 3.0-3.2) lower than the rate of heroin overdose (4.1 vs. 12.7 overdoses per 1000 injections)
Schrager 2014, USA	Cross-sectional 2009-2011	575 participants in a mixed-methods investigation into prescription drug misuse among high risk adults; mean age: 20.9 years	NMPOU in past 12 months	4	Overdose [self-reported]	Participants with overdose history were more likely to be intensive or active users rather than limited users (intensive: OR = 7.0, *P* <0.001; active: OR = 4.2, *P* <0.01) and were also more likely to be intensive than reduced users (OR=2.9, *P* <0.001)
Silva 2013, USA	Cross sectional 2009-2011	596 nonmedical users of prescription drugs; mean age: 21 years	NMPOU by injection or snorting in past 90 days	4	Non-fatal overdose	Ever snorting or sniffing drugs (OR 2.51 [1.48-4.27], *P* <0.001) and injection drug use (OR 1.68 [1.03-2.74], *P* <0.05) were associated with increased non-fatal overdose risk
Talu 2010, Estonia	Cross-sectional	350 PWID recruited using respondent driven sampling mean age: 23.9 years	Lifetime PO injection	4	Overdose [self-reported]	Fentanyl injection was associated with higher risk of lifetime overdose (AOR= 3.02 [1.65–5.54])
Tucker 2015, Canada	Prospective 2005-2013	1911 PWID; median age: 41 years	Methadone injection in the previous 6 months at baseline	1	Non-fatal overdose	Methadone injection was independently and positively associated with non-fatal overdose [AOR=1.67, (1.00–2.79)]
XX. External causes of morbidity and mortality **X60-X64: Intentional self-harm**						
Ashrafioun 2017, USA	Cross-sectional 2014	24,653 respondents in the NSDUH	Past-year NMPOU	4	Suicide attempts [self-reported]	Past-year suicide attempts were significantly associated with weekly or more NMPOU (AOR=2.03 [1.11-3.71])
Ashrafioun 2019, USA	Cross-sectional 2015-2017	45,074 respondents in the NSDUH	Past-year NMPOU	4	Suicidal ideation, planning and attempts	Past-year suicidal ideation (AOR=1.67 [1.29-2.15]), planning (AOR=1.83 [1.35-2.48]) and attempts (AOR=1.61, [1.02-2.55]) associated with NMPOU
Baiden 2019, USA	Cross-sectional 2017	8803 adolescents in the Youth Risk Behavior Surveillance System	Past-year NMPOU	4	Suicidal ideation, planning, and attempts	Past-year suicidal ideation (AOR=1.50 [1.25-1.82]), planning (AOR=1.44 [1.19-1.75]) and attempts (AOR=1.58, [1.25-2.01]) associated with NMPOU
Davis 2020, USA	Cross-sectional Not reported	889 college students	Past-year NMPOU	2	Suicidal ideation	Suicidal ideation significantly associated with NMPOU (AOR=2.21 [1.42-3.42])

Study	Study design	Participant characteristics	NMPOU exposure	Study rank	Outcome measure	Main finding and quantitative results
Guo 2016, China	Prospective longitudinal 2009-2010, 2011-2012	3273 adolescent students; mean age: 13.7	Past-year NMPOU	1	Suicide attempts [self-reported]	Baseline NMPOU was associated with reported suicide attempts at one year follow-up (AOR=2.31 [1.30-4.11])
Hakansson 2011, Sweden	Retrospective 2001-2006	1404 persons who attempted suicide; mean age of attempt repeaters: 33.5 years	Lifetime history of NMPOU	2	Suicide attempt [self-reported]	Suicide attempt repetition was associated with opioid analgesics use (OR=1.52 [1.13–2.05])
Kim-Godwin 2019, USA	Cross-sectional 2016	42,625 respondents in the NSDUH	Current NMPOU	4	Suicidal attempt, planning or ideation	Current NMPOU was significantly associated with suicide ideation (AOR=2.19 [1.44-3.33]) and suicide planning (AOR=1.98 [1.14-3.45])
Kelley 2019, USA	Cross-sectional Not reported	212 military veterans	Past-year NMPOU	4	Past 2-week suicidality (6-item scale)	NMPOU not associated with suicidality (AOR=1.03 [0.89-1.18])
Lin 2015, USA	Cross-sectional	1076 youths ages 12–18, presenting to primary care community health clinics in two urban settings	NMPOU in past 3 months	4	Suicidal attempt or ideation	PO misuse was significantly associated with suicidal thoughts or attempts (OR=2.33 [1.18–4.59])
Quinn 2019, USA	Retrospective 1994-2009	12228 respondents in the National Longitudinal Study of Adolescent Health	Lifetime NMPOU	4	Suicidality (planning and attempts)	Lifetime NMPOU associated with suicidality among males (AOR=2.10 [1.54-2.87]) and females (AOR=3.15 [2.31-4.29])
Rigg 2015, USA	Cross-sectional 2010-2013	10201 respondents in the NSDUH; 18 years or older	Past year NMPOU	4	Suicidal ideation or attempt	NMPO users were not more likely to have experienced suicidal ideation and/or attempts in the past year compared to heroin users (AOR=0.959 [0.539-1.706] *P*-value=0.887)
Roux 2008, France	Prospective 2004, 2005	111 stabilised patients receiving office-based buprenorphine; median age: 38 years	Injection PO use in last 30 days	2	Suicide attempt or ideation[self-reported]	PO injection was significantly associated with suicidal ideation or attempt (AOR=2.6 [1.2-5.7], *P*=0.02)
Samples 2019, USA	Cross-sectional 2015-2016	86,186 respondents in the NSDUH	Past-year NMPOU	4	Past year suicidal ideation, planning and attempts	Prescribed PO use associated with a significantly lower odds of suicidal ideation (AOR=0.57 [0.45-0.72]) and planning (AOR=0.53 [0.35-0.80]) but not attempts, compared to past-year NMPOU
X85-Y09: Assault						
Martins 2009, USA	Cross-sectional 2005-2006	8218 respondents in the NSDUH	Past year NMPOU	4	Assault [self-reported]	Past year opioid users were significantly more likely to have attacked someone in the past year (AOR=1.5 [1.3-1.7]), compared to users of other illegal drugs.

aHR, adjusted hazard ratio; AIRR, adjusted incidence risk ratio; ARR, adjusted risk ratio; BRFSS, Behavioral Risk Factor Surveillance System; CI, confidence interval; COMM, Current Opioid Misuse Measure; DSM, Diagnostic and Statistical Manual; ER, emergency room; HBV, hepatitis C virus; HCV, hepatitis C virus; IUGR, intrauterine growth restriction; MDE, Major Depressive Episode; MSM, men who have sex with men; NAS, Neonatal Abstinence Syndrome; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NICU, Neonatal Intensive Care Unit; NMPOU, non-medical prescription opioid use; NSDUH, National Survey on Drug Use and Health; OR, odds ratio; p-y, person years; PO, prescription opioid; PWID, persons who inject drugs; RR, risk ratio; SDS, Severity of Dependence Scale; SOAPP, Screener and Opioid Assessment for Patients with Pain; SUD, substance use disorder; TTP, Thrombotic Thrombocytopenic Purpura.