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Systematic Review

Prevalence of Pain Among Nonmedical Prescription Opioid Users in Substance Use Treatment Populations: Systematic Review and Meta-analyses

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Background: Prescription opioid analgesics (POA) are widely used in the pharmacotherapeutic treatment of acute and chronic pain in North America, where nonmedical prescription opioid use (NMPOU) has become a substantial public health concern in recent years. Existing epidemiological data suggest an association between NMPOU and pain problem symptoms in different populations, including samples in substance use treatment, although the extent of these correlations has not been systematically assessed.

Objective: To systematically review and meta-analyze the prevalence of pain symptoms or problems among populations reporting NMPOU in substance use treatment.

Study Design: Systematic review and meta-analyses.

Methods: A systematic review and meta-analyses were conducted for pain symptoms in substance use treatment samples reporting NMPOU within the last 30 days or at admission to treatment. Overall, 8 unique epidemiological studies were identified and included in the meta-analyses; in 7 of these samples POAs were the primary drug and/or POA dependence was reported.

Results: The pooled prevalence of pain in all NMPOU samples in substance use treatment was 58% (95% confidence interval [CI]: 53%–64%). The pooled prevalence of pain in the studies with POAs as the primary drug and/or POA dependence was 60% (95% CI: 52%–67%), and the prevalence of pain with "any" POA abuse (n = 2 studies) was 50% (95% CI: 40%–60%).

Limitations: A small number of studies were available and included in the review; these were restricted to cross-sectional datasets only. Statistical heterogeneity was found in the meta-analytical results.

Conclusions: Pain symptoms are disproportionately elevated in substance use treatment samples reporting NMPOU. Effective measures to prevent and treat NMPOU are urgently needed, although a substantive extent of NMPOU observed in this specific context may relate directly or indirectly to the presence of pain, e.g., either as an expression of ineffective pain care or as a consequence of previous POA-based interventions. At the same time, effective ways to treat and address ongoing pain issues in NMPOU samples need to be implemented, which may require ongoing opioid-based pharmacotherapeutic care aimed at both pain and dependence.

Key words: Prescription opioids, nonmedical use, dependence, pain, comorbidity, substance use treatment, prevention, systematic review, meta-analyses.

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Nonmedical prescription opioid use (NMPOU) as well as prescription opioid analgesic (POA) related harms – for example, morbidity and mortality – have emerged as major clinical and public health challenges in North America (i.e., the United States [US] and Canada) in recent years (1-3). For example, recent seminal surveys suggest that 5%–6% of general adult populations in North America engaged in NMPOU in the past year (4,5). In addition, there have been substantive increases in POA-related mortality (e.g., accidental poisonings) and key morbidity indicators. Specifically, the number of annual POA-related accidental deaths in the US has quadrupled, from 4,030 in 1999 to 16,651 in 2010; similarly, POA-related admissions to substance abuse treatment programs have increased from 28,326 in 2000 to 157,171 in 2010 (6-8). In Canada – while at a lower total but similar proportional levels – both POA-related mortality and substance use treatment admissions have also consistently increased in the same period (1,9,10).

The evolution of the phenomena of NMPOU and POA-related harms is influenced by several factors. In the context of POA's primary function as medications for the treatment of chronic or acute pain (11), the POA dispensing amounts have substantively increased – i.e., doubled in the US and tripled in Canada, based on defined daily doses – in North America in the past decade which far exceeds all other global regions in this regard (12). Notably, levels of POA dispensing have been found to be closely correlated with both NMPOU as well as other POA-related harm indicators on a population basis (9,13,14). Second, an emerging body of literature has shown that, among other characteristics, NMPOU is disproportionately associated with key comorbidities, including mental health and pain problems. Specifically, recent reviews of NMPOU and mental health and/or pain comorbidities in general populations have suggested that the prevalence of either comorbidity in NMPOU samples substantively exceeded respective rates in the general population (15,16).

While the link between mental health and substance abuse disorders is common and widely documented (17,18), the potential link between NMPOU and pain comorbidities is distinct and relevant for several key reasons. First, the primary medical use for POAs is pharmacotherapeutic care for pain; thus, a large proportion of individuals' initial or past exposure to POAs can be assumed to have occurred in the context of medical pain care (19-21). Chronic pain, one of the main conditions for which POAs are prescribed, are reported by 20%–30% of the general population in North America (22,23).

Second, there is evidence of considerable overlap between pain problems and NMPOU in clinical populations; specifically pain among patients in NMPOU-related substance abuse treatment (15,16). For example, Hays et al (24) found that among 162 admissions related to OxyContin abuse, 47.5% of patients reported chronic pain problems (24). Conversely, patients receiving POAs for pain treatment are at a heightened risk of developing NMPOU (25). For example, Reid et al (26) reported that POA abuse (i.e., NMPOU) occurred in 24–31% of pain patients receiving POAs in primary care (26), and 26% of outpatients on long-term opioid therapy reported current opioid dependence (27).

However, no systematic review data of the association between NMPOU and pain specifically in treatment populations have been available to date. Given the extent of NMPOU and other POA-related harms in North America, together with the need to understand potential factors and develop targeted interventions for these problems, we conducted a systematic review and meta-analyses of the associations between NMPOU and pain symptoms/problems in substance use treatment populations.

Methods

Systematic Review

This systematic review and meta-analyses followed the MOOSE (Meta-analyses of Observational Studies in Epidemiology) guidelines (28). The systematic review portion of this study identified articles that reported pain problems (in the context of a parallel systematic review on mental health problems) among patients with NMPOU in substance abuse treatment. The present meta-analyses specifically focused on the prevalence of pain among patients undergoing substance abuse treatment who had used prescription opioids nonmedically, in correlation with the specific objective of this study.

Definition of Terms

"Substance abuse treatment populations" were defined as populations in which patients were entering treatment or already in treatment for (any) substance abuse problems. Due to the range of operational definitions for NMPOU in the existing literature (29,30), NMPOU was broadly defined as any indication of nonmedical use, misuse, abuse, or dependence on POAs.

Pain problems were defined as general (rather than specific) acute and/or chronic pain problems that had been assessed either by self-report or diagnostic tools or procedures, and were not required to follow specific clinical criteria for inclusion in the review.

Search Strategy

The systematic search identified scholarly articles published from January 1, 1990, through April 25, 2012. Databases searched included MEDLINE (OvidSP; In-Process & Other Non-Indexed Citations and Ovid MEDLINE), EMBASE (OvidSP), PsycINFO (EBSCOhost), CINAHL (EBSCOhost; Cumulated Index to Nursing and Allied Health Literature), and Web of Science (Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index). Search terms consisted of both keyword and Medical Subject Headings (MeSH) (Table 1). Potentially relevant articles were retained for full-text review. Reference lists of each study identified as eligible for inclusion were hand searched in order to include any articles that may not have been captured in the electronic search. One author (AL) conducted the systematic search and initial selection of articles.

Table 1. *Example of EMBASE search strategy.*

EMBASE Search Strategy	
1	((prescri* or analges*) adj5 (opioid* or opiate*)).mp.
2	exp opiate/
3	narcotic analgesic agent/
4	(Codeine or Fentanyl or Hydrocodone or Hydromorphone or Levorphanol or Meperidine or Morphine or Oxycodone or Oxymorphone or Pentazocine or Propoxyphene or Sufentanil or Tramadol).mp.
5	1 or 2 or 3 or 4
6	(non medical or nonmedical or non-medical or aberrant or deviant or misuse or abuse or dependen* or addict*).mp.
7	self medication.mp.
8	6 or 7
9	5 and 8
10	(psychiatric disorder* or psychotic or paranoid disorder* or mentally ill or mental illness or panic disorder* or manic episode* or psychiatric symptom* or depression or depressed or depressive or mental disorder* or personality disorder* or anxiety or panic or mood disorder* or mental health).mp.
11	exp mental disease/
12	exp psychologic test/ or psychiatric diagnosis/
13	Pain.mp. or exp Pain/
14	neuralgia.mp.
15	fibromyalgia.mp.
16	exp pain assessment/
17	or/10-16
18	9 and 17
19	exp drug dependence treatment/
20	exp drug dependence/dt, rh, th [Drug Therapy, Rehabilitation, Therapy]
21	narcotic analgesic agent/dt [Drug Therapy]
22	opiate addiction/dt, rh, th [Drug Therapy, Rehabilitation, Therapy]
23	drug detoxification/
24	(((substance or drug or dependen* or addict* or opioid* or opiate*) adj10 (treat* or program or rehab*)) or detox*).mp.
25	or/19-24
26	18 and 25
27	limit 26 to yr="1990 -Current" (8869)

Selection of Studies

Articles for the meta-analyses were retained if they met the following inclusion criteria: original peer-reviewed articles published in English; patients (18 years or older) at admission or in treatment for substance abuse (excluding studies where psychiatric or pain problems were part of the inclusion or exclusion criteria); reported prevalence of NMPOU for patients within the last 30 days prior to or at admission to treatment (including any POA abuse or POA dependence); reported prevalence of pain problems or symptoms within the last 30 days prior to treatment among patients with NMPOU. If published reports drew on the same study cohort and reported the same outcome, the article with the most comprehensive data for the relevant subanalysis was included. Potentially relevant articles were discussed by AL and MR; in case of discrepancies, consensus for inclusion was reached in discussion with BF and JR.

Quality Assessment and Inter-rater Agreement

Most quality scores are tailored for meta-analyses of randomized trials of interventions (e.g., [31-33]), and many criteria do not apply to observational studies like the ones examined here. Also, their subsequent use in meta-analyses remains controversial (e.g., [34,35]). Thus, this study incorporated quality assessment differently by including quality components such as study design into the inclusion/exclusion criteria, and used meta-regression models to investigate specific study characteristics. In order to assess inter-rater agreement at the title and abstract screening phase, 2 reviewers (AL and BF) applied selection criteria to 10 abstracts randomly se-

lected from the MEDLINE search results and 10 abstracts randomly selected from the EMBASE search results.

Data Abstraction

For selected articles, the following data were abstracted: source, year(s) of baseline assessment, age at admission, proportion of men in the sample, prevalence of NMPOU (either "any" POA abuse in the last 30 days or POAs as the primary drug or POA dependence), and prevalence of pain among those reporting NMPOU. When both the prevalence of "any POA abuse" and "POA as primary drug" or "POA dependence" was available in the same article, we used both estimates in the respective subanalyses. Two reviewers (AL and MR) independently abstracted data for articles meeting inclusion criteria and discussed any discrepancies in their abstracted data to reach consensus.

Meta-analyses

We conducted a meta-analyses of all studies (n = 8) reporting pain among individuals with NMPOU in substance abuse treatment, and 2 sub-analyses of the studies of individuals with NMPOU in substance abuse treatment samples reporting either "POA as primary drug or POA dependence" (n = 7) or "any POA abuse in the last 30 days" (n = 2).

Prevalence rates were pooled across studies using inverse-variance weighted DerSimonian-Laird random-effect models to allow for between-study heterogeneity (36). We quantified between-study heterogeneity using Tau2 and I2 statistics (37). I2 can be interpreted as the proportion of the total variation in the estimated slopes for each study that is due to heterogeneity between studies. Meta-regressions focusing on key patient characteristics as independent variables, tests for publication bias or small-study effects using a visual inspection of funnel plots, and Egger's regression asymmetry test (38) were not conducted because of the small sample size of studies (39). Sensitivity analyses for the influence of single studies on the pooled prevalence estimates were conducted omitting studies one by one and re-estimating the pooled proportions. All meta-analytical analyses were conducted in Stata statistical software, version 11.2 (StataCorp LP, College Station, TX) (40).

Results

Search Results and Study Characteristics

Fig. 1 outlines the search and article selection process of this systematic review and subsequent meta-analyses. The initial electronic search yielded 14,586 articles (after manual removal of duplicates). Following the review of titles and abstracts, 340 studies were selected for full-text review. There was complete inter-rater agreement for the title and abstract screening phase. A further 331 articles were excluded for varied reasons, leaving a total of 9 studies eligible for data abstraction and inclusion in the meta-analyses. One study met the inclusion criteria, but was excluded from the quantitative analysis because the sample was restricted to pregnant women (41).

Among the 8 studies included in the meta-analyses (Table 2), 7 studies used the definition "POA is primary drug or POA dependence" (42-48), and 2 studies reported POA use to be defined as "to get high" or "taking it for the way it makes you feel and not for pain relief" (48,49). Rosenblum et al (48) included both "any POA abuse" and "POA as primary drug." Pain was defined as "chronic pain" in 4 studies (42,43,45,48), and more generally as "pain problems" in the other 4 studies (44,46,47,49). Mean age was between 30 and 45 years; the majority in most samples were men. The analyses were based on data from a total of 11,885 individuals with NMPOU in substance abuse treatment, with 6,341 reporting general pain symptoms or problems. All studies were based on North American populations, with 7 studies from the US, and one study from Canada (42).

Meta-analyses

The pooled prevalence of pain among all 8 studies (any NMPOU in the last 30 days) was 58% (95% confidence interval [CI]: 53%–64%; [Fig. 2]). The pooled prevalence of pain among the subsample of 7 studies reporting "POA is primary drug or POA dependence" was 60% (95% CI: 52%–67%) (Fig. 3). The pooled prevalence of pain among the 2 studies reporting "any POA abuse in the last 30 days," i.e., those that did not restrict their reporting to NMPOU with POA as the primary drug or POA dependence, was 50% (95% CI: 40%–60%).

The analyses detected substantial statistical heterogeneity (Table 3) as measured by I^2 and Tau^2. As per the Forest plots presented in Figs. 2 and 3, the prevalence of pain in the study samples converged at about 60%; more recently published studies utilized much larger sample sizes than earlier studies (Table 2). While the role of sample characteristics with potential clinical importance, such as age or gender, was not investigated because of the small number of primary studies, there was little variation across studies for these indicators (Table 2). Based on the sensitivity analyses, no single

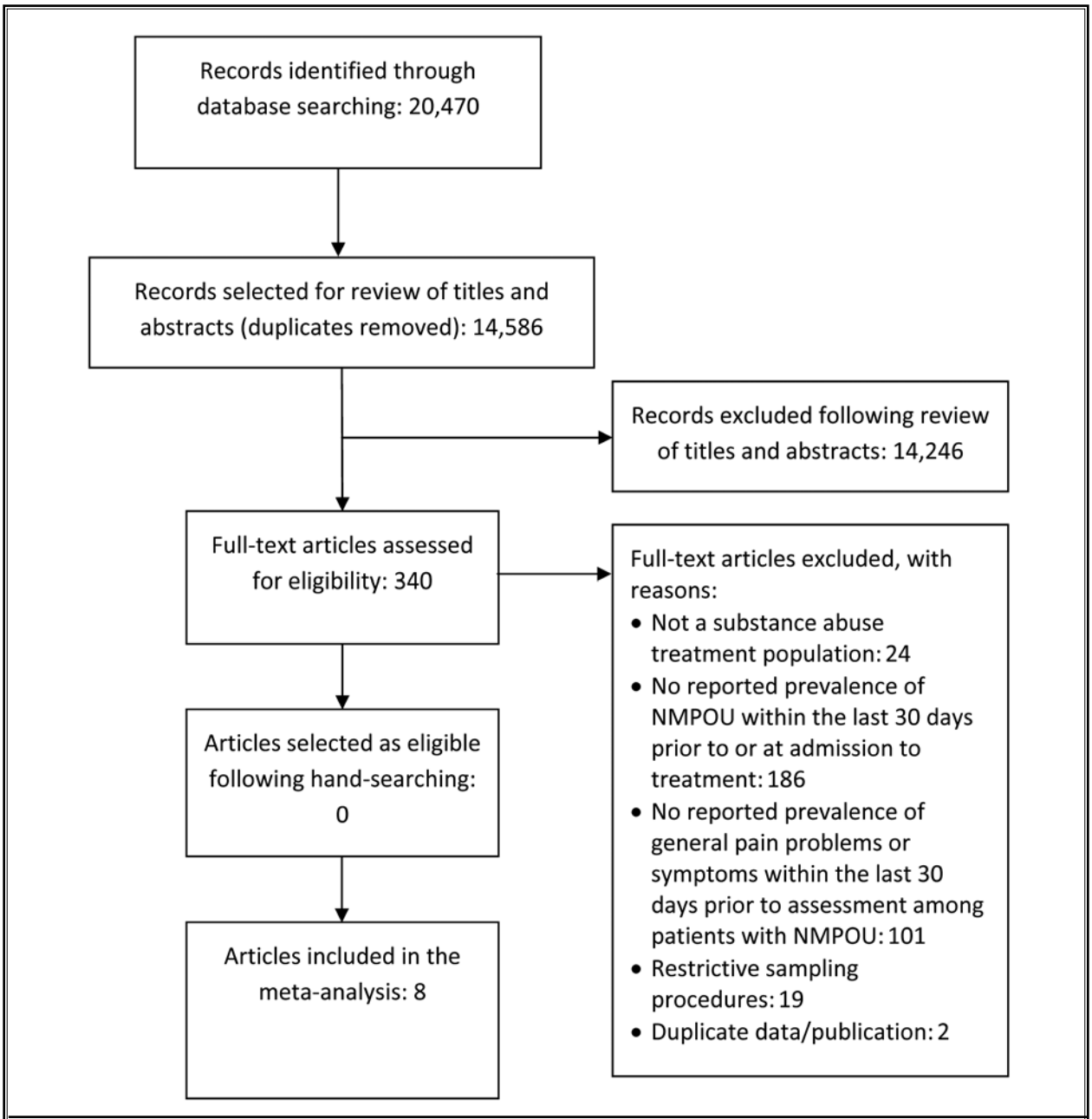

Fig. 1. Flow chart of main search strategy, article selection, and inclusion in systematic review and meta-analyses.

study had an overly large influence on the pooled effect estimates in any of the analyses.

Discussion

This systematic review and meta-analyses reviewed the evidence for the co-occurrence of NMPOU and general pain problems or symptoms in substance abuse treatment populations. The pooled total prevalence of pain was about 60% with NMPOU, with most studies reporting POAs as the primary drug for treatment involvement. The levels of pain found in the NMPOU samples are between 2- and 3-fold the prevalence levels of chronic pain documented in North American general populations, as specifically reported at 31% (US) and at 19% (Canada) (22,23).

Table 2. *List of studies and key characteristics of study populations included in the review.*

	Study	Study and Sample Details	N	Definition of NMPOU	Pain Prevalence
1	Brands et al. (42)	Retrospective chart review of all new admissions to methadone maintenance treatment at the Centre for Addiction and Mental Health (Canada) 1997-1999 Among patients with POA dependence: Mean age: 37.6 Males: 65%	Total N: 178 NMPOU: 43	POA dependence (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for opioid dependence) with no history of heroin use.	Chronic pain prior to MMT treatment: 88.4%
2	Hays (44)	Retrospective chart review of admissions to the Adult Addictive Disease Unit of a private freestanding psychiatric facility in Kentucky (USA) 2000-2002 Among patients dependent on OxyContin: Mean age: 31.0 Males: 72.2%	Total N: 579 NMPOU: 187	OxyContin dependence	Pain problem at admission: 35.3%
3	Passik et al. (45)	Prospective survey of prescription drug abusers entering the Ridge Behavioral Health Addiction Unit in Kentucky (USA) Mean age: 30.95 (SD=10.21) Males: 69%	Total N & NMPOU: 109	Structured Clinical Interview for DSM-IV (SCID), and POA Abuse Survey. "[P]atients whose chief complaint was prescription drug abuse were enrolled" (Passik et al. 2006, p.7). "All patients met criteria for current opioid abuse and or dependence" (Passik et al. 2006, p.8). "All of the subjects (n = 109, 100%) reported abusing prescription opioids, which was corroborated by their urine toxicology and blood serum tests" (Passik et al. 2006, p.8).	Chronic pain concerns corroborated by the medical record: 60.6%
4	Torrington et al. (46)	Opiate dependent patients entering office-based buprenorphine treatment (USA) 2003-2005 Among patients reporting POA as their primary drug of abuse: Mean age: 44.71 (SD=11.81) Males: 45%	Total N: 101 NMPOU: 42	DSM-IV criteria for opioid dependence. POA was the primary opiate of abuse based on self-report and urine toxicology screen.	Self-report of pain management as reason for treatment: 73.8%
5	Rosenblum et al. (48)	Multi-state survey of patients with opioid dependence at admission to 72 methadone maintenance treatment programs (USA) 2005 Mean age: 35.0 (SD=10.6) Males: 63.4%	Total N: 5663 NMPOU: POA use during the past 30 days to get "high": 3797 POA primary drug: 2174	POA use during the past 30 days to get "high" POA is primary drug: "drug you used the most to get high with before coming to this methadone program" (Rosenblum et al. 2007, p.65).	Chronic pain (moderate to very severe and persisting 6 or more months) among those using POAs during the past 30 days to get "high" (n=3702): 45% Chronic pain (moderate to very severe and persisting 6 or more months) among POA primary drug users (n=2122): 46.6%

Table 2 (cont.). *List of studies and key characteristics of study populations included in the review.*

	Study	Study and Sample Details	N	Definition of NMPOU	Pain Prevalence
6	Cicero et al. (43)	Survey of patients entering treatment for POA abuse (USA) Mean age: 34.79 Males: 55%	Total N & NMPOU: 1408	"DSM-IV criteria for substance abuse whose primary drug was a prescription opioid (i.e., not heroin); and…use of prescription opioid drugs to get high at least once in the past 30 days prior to treatment" (Cicero et al. 2008, p.129).	Chronic pain: 61.5%
7	Green et al. (49)	Addiction Severity Index Multimedia Version Connect (ASI-MV® Connect) database of people entering 220 substance abuse treatment centers (USA) 2005-2008 Mean Age: 34.9 (SD=11.6) Males: 61%	Total N: 29,906 NMPOU: 3,821	POA abuse: self-report of past 30 day use of any POA "in a way not prescribed by your doctor, that is, taking it for the way it makes you feel and not for pain relief"(Green et al. 2009, p.66).	Self-reported pain problem, past 30 days: 54.9%
8	Cicero et al. (47)	Self-administered survey of patients entering drug treatment programs whose primary drug was a POA (USA) 2008-2010 Mean Age: 35 Males: 48.2%	Total N & NMPOU: 2,573	"DSM-IV criteria for substance abuse whose primary drug was a prescription opioid (i.e., not heroin); and…they used prescription opioid drugs to get high at least once in the past 30 days prior to treatment" (Cicero et al. 2012, p.88).	Moderate to severe non-withdrawal pain in the last 7 days: 58.7%

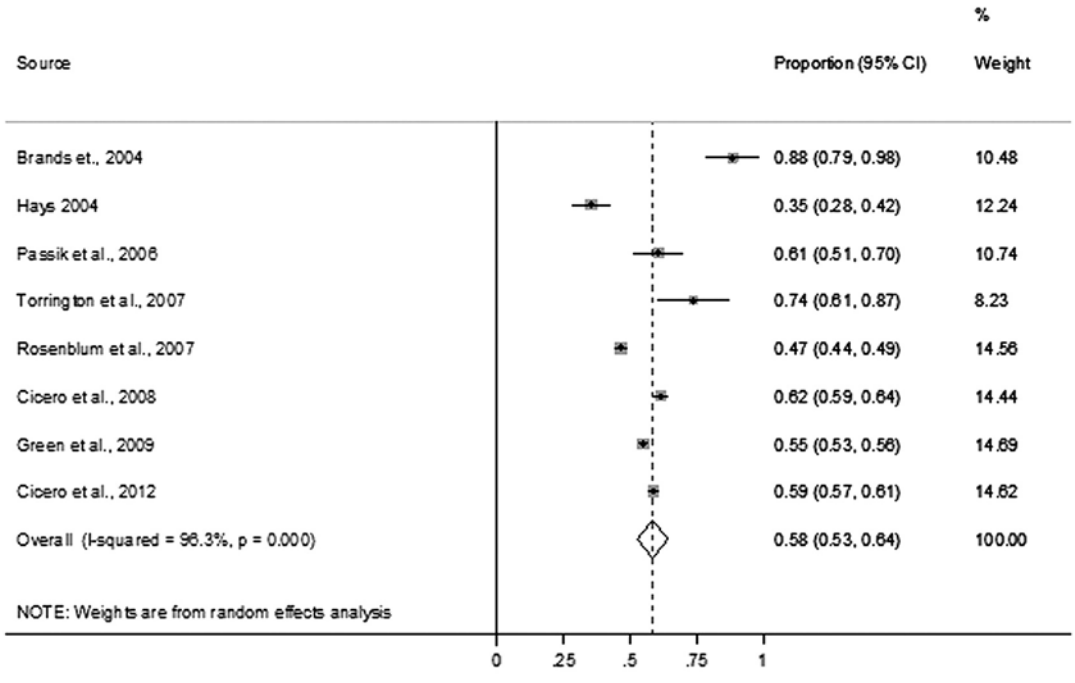

Fig. 2. *Forest plot of the random effects meta-analyses of the prevalence of pain in NMPOU (including POA as "primary" drug, POA dependence, or "any" POA abuse) in substance abuse treatment populations.*

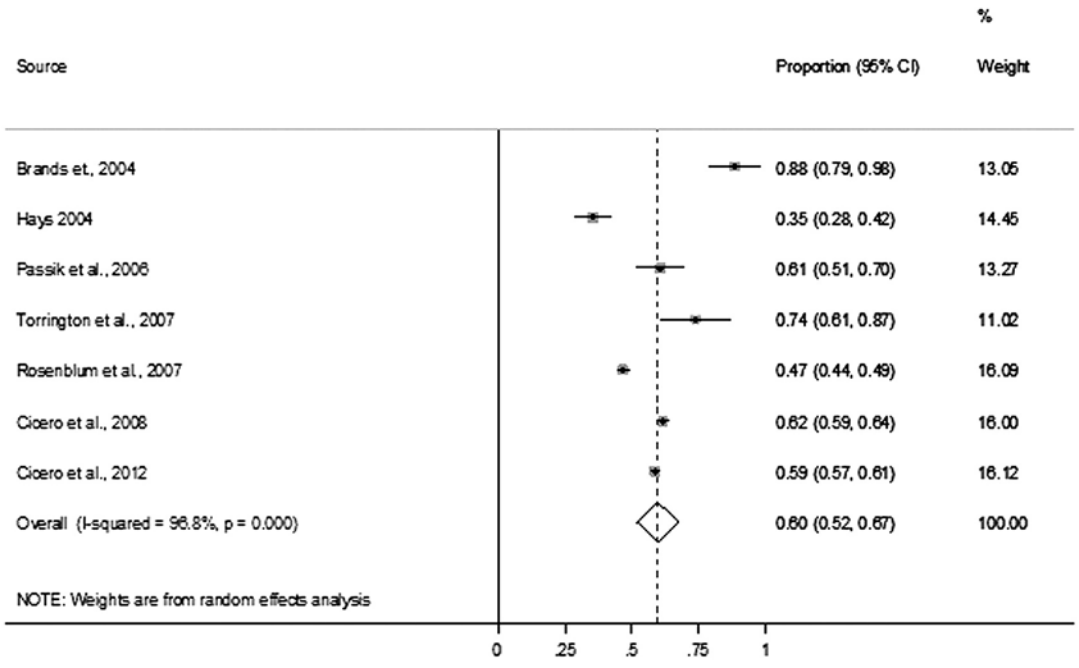

Fig. 3. *Forest plot of the random effects meta-analyses of the prevalence of pain in NMPOU (reporting POA as "primary" drug or POA dependence) in substance abuse treatment populations.*

Table 3. *Heterogeneity analysis results of studies reporting pain included in the meta-analyses.*

Meta-analyses	Number of Studies	*P* Value for Heterogeneity	I^2	Tau^2
All studies	8	$P < .0001$	96.3%	.0057
POA is primary drug or POA dependence	7	$P < .0001$	96.8%	.0096
"Any" POA abuse	2	$P < .0001$	98.7%	.0048

This study has some potential limitations. First, this review only relied on cross-sectional datasets, thus limiting the overall quality of evidence available for analyses, specifically in respect to exploring potential sequential or causal relationships between NMPOU and pain. Second, pain problems had been assessed by diverse methods in the study populations, including self-report, potentially limiting the systematic quality or reliability of these data. Pain, in fundamental terms, is a complex and multidimensional phenomenon to define and measure; it may be reflective of rather subjective states or experiences – involving both strictly physical as well as other, e.g., emotional or cognitive, levels – and its experience may be influenced by a variety of key covariates or modulators (50-52). Our analysis detected substantial statistical heterogeneity in regards to our meta-analytical results, reflecting the relatively high between-study differences compared to the small standard errors of the original studies. Given the different operation modes of both pain and NMPOU as described, the relatively high between-study variability might be expected. Another possible explanation could be distinct ecological factors such as availability of substance abuse treatment or availability of POAs for NMPOU. Because of the small number of studies available, we could not further investigate this heterogeneity quantitatively; however, in only one of the primary studies was pain prevalence below 47%. Thus, the prevalence of pain was large in almost all studies examined.

A few studies have assessed a heterogeneous array of motives for NMPOU, including pain relief, intoxication, experimentation, relaxation or stress relief, dealing with emotional or anxiety problems, and preventing opioid withdrawal (53-55). On this basis, "nonmedical use" of POA may serve a quasi-medical or

self-help function to a considerable extent, with the desire to relieve "pain" – however defined or experienced – as consistently one of the most predominant motives cited (55,56). Reflecting this context, our analyses found high levels of pain problems in NMPOU samples in substance use treatment populations, although it was by far not reported universally, as one would expect if pain relief was seen as the exclusive reason for (medical or nonmedical) POA use. Nevertheless, the levels of pain problems or symptoms observed in the NMPOU samples far exceed the prevalence of pain observed in relevant general population comparisons, suggesting a strong contributing factor or role in the NMPOU outcomes. In the context of the widespread and increasing medical use of POA for analgesic care in North America, large proportions of individuals reporting NMPOU have histories of medical use or sourcing of POAs (20,21,26,27,57). In the one study of individuals in treatment for NMPOU included in the present review which presented relevant data, 79% of men and 85% of women had their first exposure to POAs through a legitimate prescription from a doctor; 85% cited pain as the initial reason for POA use (43).

While our review does not provide systematic insights on the causal or sequential relationship between NMPOU and pain, and relied principally on cross-sectional observations, the potential extensive overlap of medical POA use exposure and subsequent NMPOU points to a variety of possible key etiological dynamics. First, given the known psychopharmacological properties of POAs (58,59), prolonged medical exposure to POAs may lead to habit and tolerance formation, potentially resulting in POA misuse, abuse, or dependence. The interactive dynamics between pain and NMPOU may further be amplified by the neurobiological effects of hyperalgesia, suggesting that prolonged exposure to POAs may – paradoxically – increase sensitization to pain and hence amplify the need or desire for more or better therapeutic relief, creating a vicious cycle of sorts (60,61). Related to this is an individual's categorical experience or form and intensity of pain perception may be affected by POA dependence, or mental health problems – which have been documented to disproportionately co-occur with POA use and NMPOU (16,62,63) – as the neurocognitive mechanisms underlying pain are subject to modulation and may be influenced by these factors (64-67).

On this basis, a substantial proportion of NMPOU in individuals with pain problems may occur – or at least have been initiated – as a form of "self-medication," primarily to address their pain symptoms or problems (16,68-70). In "POA-rich" environments like North America, "self-medication" with POAs is easily done, regardless of whether medical sources are available or not. The common occurrence of self-medication involving POAs may not be surprising, given the prevalent, complex, and debilitating nature of acute or chronic pain problems. Conversely the availability of specialized pain care, as well as the effectiveness of treatment options for chronic painare limited (71-75). The potentially widespread occurrence of "self-medication" or quasi-therapeutic usage of POA may also be supported by data indicating that among general population samples of NMPOU, only a small proportion report doing so in order to "get high" or to intoxicate themselves (5).

A crucial question arising then is what possible measures or interventions are available to reduce NMPOU, specifically in populations with co-occurring pain problems. On a population level, the levels of POA use and POA-related problems (e.g., NMPOU) are closely correlated (13,14,76). Given that overall POA use levels in North America (the context of all studies included in the present review) are far higher than elsewhere, general reductions in POA use in North America would likely facilitate a decrease in corresponding POA-related problem outcomes, including morbidity (e.g., NMPOU), on a population basis. While reductions in medical POA use would need to be prudently selective, targeting those cases where POA therapy is not adequately indicated or unlikely to be effective, where there is evidence of overly generous or potential over-prescribing of POAs (77-79), as well as the mixed evidence on the efficacy of POA treatment for chronic pain (58,80,81), should strongly encourage fundamental reviews of current clinical POA use guidelines and practices.

The considerable extent of NMPOU that leads to the need for substance use treatment – as per our data – is indeed not just associated but it causally linked to pain problems which are not otherwise or effectively treated. This may signal a system-level problem in current approaches to pain treatment. Various factors have been identified that may diminish the effectiveness of currently available pain treatment and optimal treatment approaches. Those involving multifaceted treatment components are not widely available (82). It is possible that current pain treatment may not be effective in adequately reducing pain, either due to limited effectiveness, undertreatment, or restricted pain care availability or access which may need to be addressed on a system level; these issues are widely and controversially debated

(78,83,84). Conversely, most measures to date aimed at reducing NMPOU in the specific contexts of clinical pain treatment have focused on the individual patient's "risk" characteristics for NMPOU, for example, by way of clinical screening or assessment tools to predict pain patients' POA abuse risk or liability within a paradigm of "universal precautions" (85-91). While an individual history of other (e.g., alcohol) psychoactive drug abuse appears to be the strongest predictor of NMPOU, the psychometric and predictive properties of the risk assessment tools available have been characterized as weak and inconclusive (25,57).

There is also concern that the primary focus on pain patients' POA abuse liability may primarily stigmatize or exclude from pain care those individuals with substance use histories, even though these patients are known to commonly have elevated levels of pain problems which can be managed effectively with appropriate approaches (92-95). Another proposed intervention are POA formulations designed to resist or deter abuse, although their effectiveness is limited (89,96). Overall, considerable work remains to be done towards more effective prevention and recognition of NMPOU among pain care patients (25,61,97,98). One simple but important avenue in clinical practice to reduce potential pain-related NMPOU — especially following initial POA exposure in the context of pain treatment — is improved monitoring or aftercare for pain symptoms or problems, especially after POA-based therapy has been completed or terminated.

The other key challenge is how to appropriately address co-occurring pain problems among individuals with NMPOU. Especially in the context of substance abuse treatment, abstinence from POAs may appear as a primary objective. However, this does not address or could possibly worsen a patient's pain experiences. Combined with negative experiences of opioid withdrawal, cravings, etc., abstinence could contribute to or further amplify possible NMPOU (70,99,100). In addition, the evidence for abstinence-oriented treatment interventions (e.g., detoxification) among POA-dependent individuals is rather limited, even when pain is not a universal or primary factor (101,102).

Many POA-dependent individuals with persistent pain problems are thus likely best cared for by opioid maintenance treatment, e.g. either methadone or buprenorphine maintenance (101,103,104). As these opioid maintenance treatment medications also have analgesic effects, they may help to address these co-existing pain comorbidities, although additional POA-based pharmacotherapy may be required to respond to patients' pain problems (95,105,106). Overall, from both a clinical as well as a public health perspective, it appears preferable to aim to effectively address patients' opioid dependence and pain problems (e.g., through tightly structured and monitored POA therapy combined with ancillary support and interventions (94,95,107) through opioid maintenance treatment and complementary pain care interventions rather than prioritizing abstinence from POAs. These complex issues involving dependence, pain, and quite commonly mental health problems require careful assessments and intervention planning on a case-by-case basis in clinical practice, ideally by multi-disciplinary expert teams; however these teams are not commonly available (94,108).

Based on the above discussion of findings, a number of key issues require further targeted research. First, more and better – both retrospective and prospective – studies and data are needed documenting individuals' trajectories between legitimate POA prescription or pain care, and substance abuse treatment for NMPOU. Second, more systematic investigations are needed among individuals reporting NMPOU – in as well as outside of treatment settings – what role pain, or forms of "self-medication" for pain may play in NMPOU behavior. Third, the interplay of pain and dependence, as well as potentially co-occurring mental health factors, ought to be more systematically explored on both neurobiological as well as experiential and/or behavioral levels. Finally, data are needed in regards to treatment options and outcomes for individuals with NMPOU (e.g., dependence) and pain problems.

In sum, in the context of high levels of NMPOU, and growing POA-related morbidity and mortality in North American populations, pain problems evidently constitute major, yet complex covariate factors. While more effective ways and methods need to be developed to reduce the risks of NMPOU in the contexts of pain and/or pain care, those individuals with co-occurring NMPOU and pain require adequate and effective care for these comorbidities, for which the best interventions and practices remain to be developed and implemented.

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