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Review

The source and diversion of pharmaceutical drugs for non-medical use: A systematic review and meta-analysis

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ABSTRACT

Background: The non-medical use (NMU) of pharmaceutical drugs is an increasing public health concern. This systematic review consolidates current knowledge about how pharmaceutical drugs are obtained for NMU and the processes and people involved in diversion.

Methods: Peer-reviewed and grey literature databases were searched for empirical studies published between 1996 and 2017 that examined the source or diversion of pharmaceutical opioids, sedatives or stimulants for NMU in countries with reported misuse problems. Pooled prevalence meta-analyses using random effects models were used to estimate the prevalence of medical and non-medical sourcing reported by end-users, and gifting, selling and trading by various populations.

Results: This review synthesizes the findings of 54 cross-sectional studies via meta-analyses, with a remaining 95 studies examined through narrative review. Pharmaceutical drugs are primarily sourced for NMU from friends and family (57%, 95% CI 53%–62%, I^2 = 98.5, n = 30) and despite perceptions of healthcare professionals to the contrary, illegitimate practices such as doctor shopping are uncommon (7%, 95% CI 6%–10%, I^2 = 97.4, n = 29). Those at risk of diversion include patients displaying aberrant medication behaviors, people with substance use issues and students in fraternity/sorority environments. Sourcing via dealers is also common (32%, 95% CI 23%–41%, I^2 = 99.8, n = 25) and particularly so among people who use illicit drugs (47%, 95% CI 35%–60%, I^2 = 99.1, n = 15). There is little to no organized criminal involvement in the pharmaceutical black market.

Conclusion: Pharmaceutical drugs for NMU are primarily sourced by end-users through social networks. Future research should examine how dealers source pharmaceutical drugs.

1. Introduction

Pharmaceutical non-medical use (NMU) involves the consumption of a prescription or over-the-counter (OTC) drug for non-therapeutic purposes or other than directed by a healthcare professional (HCP) (Barrett et al., 2008; Larance et al., 2011b; Nielsen et al., 2008; Sembower et al., 2013). The prevalence of pharmaceutical NMU now rivals the use of illicit drugs in many developed countries around the world. For instance, general population surveys conducted in the United States (US), Canada and Australia have found that the NMU of pharmaceutical opioids is second only to the illicit use of cannabis (Australian Institute of Health and Welfare (AIHW), 2017; Center for Behavioral Health Statistics and Quality, 2015; Health Canada, 2012; Office of National Drug Control Policy, 2011).

The health, social and economic costs of the NMU of pharmaceutical drugs are well documented. The health risks range from fatal and non-fatal overdose to intoxication and dependence (Kaye and Darke, 2012; Olfson et al., 2015; Saha et al., 2016). In addition, poly drug use − the misuse of pharmaceutical drugs in combination with alcohol or other drugs − can magnify these problems and result in an increased risk of serious adverse consequences such as death (McCabe et al., 2006a; UNODC, 2017). Recent data indicates that pharmaceutical opioid-related deaths are increasing in Australia (Australian Bureau of Statistics, 2017), Canada (Canadian Institute of Health Information, 2017), the US (UNODC, 2017) and the UK (Office for National Statistics, 2017). In the US, the NMU of pharmaceutical opioids has been estimated to cost over

Abbreviations: ADHD, attention deficit hyperactivity disorder; AIHW, Australian Institute of Health and Welfare; HCP, healthcare professional; NCJRS, National Criminal Justice Reference Service (US); NMU, non-medical use; OST, opioid substitution therapy; PMP, prescription monitoring programs; PWUD, people who use drugs; UK, United Kingdom; UNODC, United Nations Office of Drugs and Crime; US, United States

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$70 billion annually (Florence et al., 2016). The harms related to the NMU of sedative and stimulant drugs are also well documented and include dependence, hospitalization and death (Australian Bureau of Statistics, 2017; Australian Institute of Health and Welfare (AIHW), 2017; National Institute on Drug Abuse, 2017; Sussman et al., 2006).

Pharmaceutical drugs for NMU may be sourced directly from medical sources via a prescription or OTC from a pharmacy, or from non-medical sources such as friends, relatives, a dealer or online (Substance Abuse and Mental Health Services Administration, 2017). The process of accessing pharmaceutical drugs for NMU involves diversion, whereby pharmaceuticals are channeled from legal sources to the illicit marketplace for NMU (Inciardi et al., 2007b). There is a large evidence base concerning the diversion of pharmaceutical drugs. Diversion is believed to occur through a number of mechanisms such as doctor or pharmacy shopping, prescription forgery, illegal sale, theft, internet sales, sharing among family and friends, and over-prescribing by HCP (Ford and Lacerenza, 2011; Fountain et al., 1997; Inciardi and Cicero, 2009; Inciardi et al., 2009b; Inciardi et al., 2007b; Parran and Grey, 2000; Rodwell et al., 2010). In light of the prominence of pharmaceutical NMU and the associated costs, it is timely to consolidate what is known about sourcing and diversion. This is critical for informing the development of effective prevention, treatment and law enforcement interventions (Ritter, 2005).

To date, reviews of this topic have canvassed issues related to the demand for pharmaceutical drugs without examining source and diversion (Lofwall and Walsh, 2014; Mounteney et al., 2015) or focused on one particular drug class (Kaye and Darke, 2012; Manchikanti et al., 2010) or diversion mechanism (Nielsen and Barratt, 2009). Further, most of the reviews have examined the problem as it occurs only in the US (Fischer et al., 2010; Inciardi and Cicero, 2009; Inciardi et al., 2009b), despite increasing concerns elsewhere. In order to carve a path for future research and policy efforts, this review seeks to consolidate what is known about the source and diversion of pharmaceutical drugs for NMU in Australia, Canada, Europe, the UK and the US.

2. Method

This review was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (PRISMA Statement, 2015).

2.1. Search strategy

With the assistance of a librarian trained in systematic review methodologies, searches were conducted in seven peer-reviewed and grey literature databases: MEDLINE, EMBASE, PsycINFO, CINCH, Criminal Justice Abstracts, Drug database: DRUG and the US National Criminal Justice Reference Service (NCJRS). The detailed search strategy used for each of these databases is provided in Appendix A of the supplementary . Three groups of search terms were developed and Boolean operators were used to separate each term (OR) and each group (AND):

1 Pharmaceuticals, medication, prescri* (-ption, -bed), prescription drug, therapeutic drug, non-prescription drugs, over-the-counter, opioid, analgesic, stimulant, benzodiazepine, barbiturate, sedative, tranquiliser/zer; (AND)
2 Supply chain, supply, supplier, diversion, drug diversion, sourcing routes, source, drug market, drug trade, drug trafficking, Dark Web, Dark Net, Internet, doctor shopping, pharmacy shopping, drug dealing, on-selling, over-prescribing, theft, fraud; (AND)
3 Non-medical use, misuse, illicit use, recreational use, abuse, poly drug use.

For MEDLINE, EMBASE, PsycINFO and Drug database: DRUG, the search terms were mapped to the associated subject headings, in addition to keyword searches for specific phrases. For CINCH, Criminal Justice Abstracts and the NCJRS, keyword searches only were used.

Additionally, a number of selected websites were searched for relevant grey literature. International websites included: UNODC, the Center for Disease Control and the World Health Organization. Australian websites included: Australian Policy Online, Australian Institute of Criminology, NSW Bureau of Crime Statistics and Research, AIHW, Australian Criminal Intelligence Commission and the National Drug and Alcohol Research Centre.

Reference lists in retrieved articles were also scanned to identify any relevant studies not captured. Citations were managed using the bibliographic software EndNote with duplicates removed manually.

2.2. Study selection

Inclusion and exclusion criteria were developed, with a focus on including empirical quantitative and qualitative studies that contained content relating to the source or diversion of pharmaceutical drugs that are most often subject to NMU, namely pharmaceutical opioids (full agonists like oxycodone and partial agonists like buprenorphine), sedatives (barbiturates, benzodiazepines and benzodiazepine-like drugs or ‘z-drugs’) and stimulants.

The searches were limited to ‘humans’ and the English language, and published between 1996 and 2017 (22 years). The lower cut-off was chosen because it aligns with the increased prescribing and misuse of pharmaceutical opioids in the US (King et al., 2014), and to focus on results in the past two decades so that findings are most relevant to current policy and practice. For comparability, studies from Australia, Canada, Europe, the UK and the US were included in the review. Although challenges relating to the NMU of pharmaceuticals in developing countries are equally important, the supply issues experienced are different and warrant separate analysis that is outside the scope of this review.

Literature was also excluded if it focused on the supply of illicit drugs (e.g., marijuana, cocaine, heroin) with no mention of pharmaceuticals; or focused only on the trends or prevalence of NMU, in the absence of any focus on source or diversion. Reviews, editorials, commentaries, letters or notes, opinion pieces and media articles were also excluded.

2.3. Data extraction and quality assessment

A standardized coding form was developed to ensure that consistent information was extracted from each study, including: author, year, country of origin, methodology, study design, sample size, target population, prescription drug class and key findings relating to the source and diversion of pharmaceutical drugs.

A modified version of the Checklist for the Evaluation of Research Articles (Parts V and VI) developed by DuRant (1994) was used to assess the quality of the cross-sectional studies included in the meta-analyses (Pont et al., 2009). A score of 1 was given for ‘YES’ responses and 0 for ‘NO’, thus a higher score indicates better methodological quality. Studies with a high score were strong in their sample description, including detailed inclusion criteria and demographic characteristics of the sample and had sample sizes of greater than 100. Stronger studies also employed validity or reliability testing of the survey instruments and achieved a response rate of greater than 80%, indicating lower risk of bias. The statistical procedures employed in the higher quality studies were clearly described and involved multivariate analyses. The modified appraisal tool and detailed scoring for each study is provided in Appendices B and C.

2.4. Data synthesis

To synthesize the findings of the cross-sectional studies that examined the source of pharmaceutical drugs for NMU, several meta-

analyses were performed using a random-effects model using the MetaXL add-in for Microsoft Excel (Barendregt, 2016). A pooled prevalence figure was calculated with 95% confidence intervals for each source. Similarly, the cross-sectional studies that examined the prevalence of diversion by gifting, selling and trading among different populations groups were synthesized via random-effects meta-analyses in MetaXL. A random-effects model was used to account for heterogeneity (Schroll et al., 2011). Pooled prevalence meta-analysis is a useful tool for synthesizing information from similar studies and it is often used in epidemiology to estimate the prevalence of disease. It has been used in this review to highlight patterns in pharmaceutical sourcing and diversion for NMU as reported in cross-sectional surveys. As the surveys allowed respondents to select multiple sources (e.g., friends, online) and diversion mechanisms (e.g., gift, sell), several meta-analyses were required to determine the prevalence of each. Potential causes of heterogeneity were explored by carrying out sensitivity testing and subgroup analyses, where possible.

The results section presents the meta-analyses results, followed by a discussion of any pertinent findings of the subgroup analyses for population group and drug type. The remaining studies were examined through narrative synthesis and have been used to help explain or elaborate upon the findings from the meta-analyses.

3. Results

3.1. Searches

A total of 2012 records were initially identified as potentially relevant from the database and website searches (Fig. 1). Across the seven databases and manual searches, 215 records were deemed relevant and full-text were accessed. Of these, 66 were excluded primarily for being non-empirical or lacking information on the source or diversion of pharmaceutical drugs for NMU. Appendix D provides a list of all excluded articles with reasons. A total of 149 records were included in the narrative review and 54 studies were also synthesized using meta-analysis.

3.2. Study characteristics

Most studies were published post-2007 (73.8%) and conducted in the US (58.4%) and Australia (20.8%; Appendix E). Two-thirds (65.8%) examined the source of pharmaceutical drugs for NMU, while under half (43.6%) studied diversion (Table 1). The vast majority of the source studies focused on where pharmaceutical drugs are obtained by the end-user, with very few studies focusing on sources used by dealers. The diversion studies examined diversion by gifting, selling or trading pharmaceutical drugs among different population groups, the risk factors for diversion, and the criminality involved in diversion activities. Appendix H provides a list of the included studies and their characteristics.

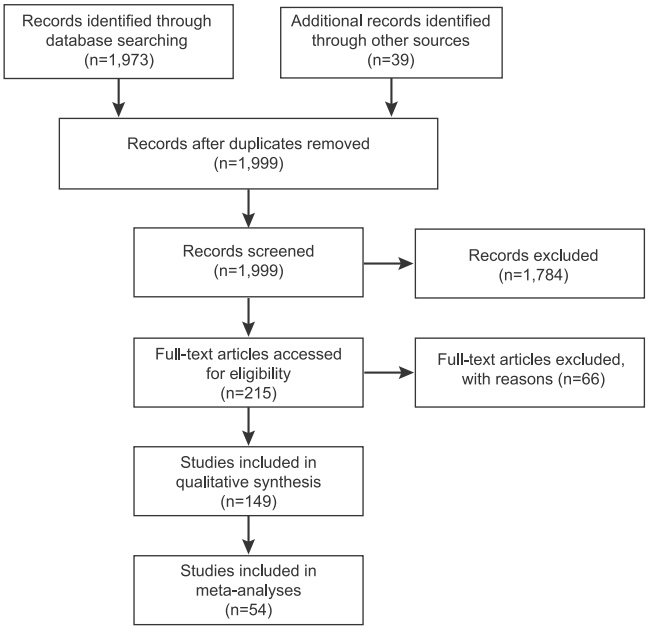


Fig. 1. Search results.

Table 1
Study characteristics.

	Total studies (n = 149) n (%)	Source studies (n = 98) n (%)	Diversion studies (n = 65) n (%)
Target population			
People who use drugs (PWUD)	65 (43.6)	55 (56.1)	22 (33.8)
Students	20 (13.4)	8 (8.2)	13 (20.0)
General population	17 (11.4)	15 (15.3)	3 (4.6)
Patients or prescription holders	17 (11.4)	7 (7.1)	10 (15.4)
Key experts or professionals	16 (10.7)	4 (4.1)	12 (18.5)
Prison population	5 (3.4)	3 (3.1)	2 (3.1)
Prescription drug dealers	4 (2.7)	2 (2.0)	2 (3.1)
Healthcare professionals[a]	4 (2.7)	–	4 (6.2)
No target population[b]	10 (6.7)	9 (9.2)	1 (1.5)
Drug class			
Opioids[c]	96 (64.4)	73 (74.5)	33 (50.8)
Stimulants	42 (28.2)	27 (27.6)	18 (27.7)
Sedatives[d]	37 (24.8)	32 (32.7)	9 (13.8)
Barbiturates	4 (2.7)	3 (3.1)	1 (1.5)
Benzodiazepines	36 (24.2)	30 (30.7)	8 (12.3)
Z-drugs	8 (5.4)	5 (5.1)	4 (6.2)
General[e]	27 (18.1)	10 (10.2)	17 (26.2)
Study type			
Cross-sectional survey	105 (70.5)	67 (68.4)	50 (76.9)
Qualitative/ethnography	32 (21.5)	19 (19.4)	2 (3.1)
Cross-sectional other[f]	16 (10.7)	13 (13.3)	16 (24.6)
Cohort	7 (4.7)	7 (7.1)	–

Studies may examine multiple populations or drug classes and adopt multiple methodologies, so totals do not add to 100%. Source and diversion studies are not mutually exclusive.

[a] Involved in diversion or misappropriation from the workplace, not as key experts or informants.

[b] Includes studies that did not sample a specific population, such as observational studies of Internet forums.

[c] Full agonists (e.g. oxycodone) and partial agonists (e.g. buprenorphine).

[d] Barbiturates (e.g, phenobarbital), benzodiazepines (e.g. alprazolam) and benzodiazepine-like drugs or 'Z-drugs' (e.g. zopiclone).

[e] Includes studies that examined the source or diversion of prescription drugs, with no specification of drug type.

[f] Includes other cross-sectional data such as information collected from Internet forums and websites.

3.3. Source of pharmaceutical drugs for NMU

Of the 98 studies that examined the source of pharmaceutical drugs for NMU, 67 (68.4%) included a cross-sectional survey component. Thirty-four (34.7%) surveyed people who misuse pharmaceutical drugs about all sources of obtainment and contained comparable data for meta-analysis (Table 2).

The remaining 33 (33.7%) cross-sectional studies were excluded from the meta-analyses for focusing only on sources involving monetary exchange (8), reporting on the most recent or usual source of pharmaceutical drugs (as opposed to any source) (6), not specifying drug type (6), surveying people about the price of pharmaceuticals (5), focusing only on illegal or high-risk sources (3), lacking adequate detail

Table 2
Prevalence of pharmaceutical sourcing for NMU, studies included in the meta-analyses.

	Author (Year)	Target population	Quality score	Drug class	Sample size (n)	Source						
						Friend or family (free)[a] (%)	Friend or family (buy) (%)	Legitimate medical source (%)	Illegitimate medical source[c] (%)	Internet (%)	Dealer or street market (%)	Theft[b] (%)
1	Barrett et al. (2005)	Students (University)	9	ST	36	78		11			17	4
2	Bazazi et al. (2011)	PWUD (Opioids, in treatment)	9	O (BP)[d]	100	36					24	
3	Boyd (2006)	Students (Secondary)	13	O	139	34				0		
4	Bruno (2007)	PWUD (Injecting, in treatment)	7	SD	81	65	37	64	5		21	0
5	Cassidy et al. (2015b)	General population (Adults 18–49 years)	13	ST	224	91		11	5		20	10
6	Cassidy et al. (2015a)	PWUD (In treatment)	11	O	29,253			50			28	
	Cassidy et al. (2015a)		11	ST	1905	54		23			24	
7	Chen et al. (2014)	General population (Adolescents, adults)	13	ST	4945	53	18	10	3	2	7	5
8	Cicero et al. (2008)	PWUD (Opioids, in treatment)	8	O	1116	59		59		6	65	21
9	Cicero et al. (2011)	PWUD (Opioids, in treatment)	13	O	1983	20		25			58	5
	Cicero et al. (2011)		13	O	782	55		14	13		67	11
10	Daniulaityte et al. (2014)	PWUD (Opioids, out of treatment)	12	O	383	88	80	47	10	1		21
11	Davis and Johnson (2008)	PWUD (Out of treatment)	8	O (OXY)	80			38			63	
	Davis and Johnson (2008)		8	O (MET)	55			14			75	
12	DeSantis et al. (2008)	Students (University)	9	ST	585	87					8	
13	DeSantis et al. (2009)	Students (University)	9	ST	170	100					9	
14	Dupont et al. (2008)	Students (University)	10	ST	110	90						
15	Festinger et al. (2016)	PWUD (Pharmaceuticals, in treatment, adolescents and adults)	11	O	970					2		
	Festinger et al. (2016)		11	SD	609					1		
	Festinger et al. (2016)		11	ST	705					2		
16	Ibañez et al. (2013)	PWUD (Pharmaceuticals, in and out of treatment)	12	SD	1207	52		11	3		65	6
17	Inciardi et al. (2010)	PWUD (Opioids, in treatment)	12	O	4008	52		41	6	3	62	15
	Inciardi et al. (2010)	PWUD (OST, in treatment)	12	O	9008	44		23	2	2	78	5
	Inciardi et al. (2010)	Students (University)	12	O	116	53		39		2	20	6
18	Katz et al. (2008)	PWUD (Pharmaceuticals, out of treatment)	11	O	896	60		20	5	5	80	15
19	Kaye et al. (2014)	PWUD (Psychostimulants, in and out of treatment)	11	ST	83	71		7			16	
20	Levy (2007)	PWUD (In treatment)	7	O	204	70	4	14				
21	Martins et al. (2009)	General population (Adolescents,	13	O	285	64	58	21	12	1	35	25
	Martins et al. (2009)	adults)	13	O	2954	61	15	23	5	3	8	10
22	McCabe et al. (2007)	Students (University)	13	O	640	41				0	4	
23	McCabe et al. (2013)	Students (Secondary)	13	O	647	55	38	37		1	19	22
24	Monte et al. (2009)	PWUD (Opioids, in treatment)	7	O (BP)[d]	49	61					39	
25	Ng and MacGregor (2012)	Police detainees	7	O (BP)[d]	44	48	18		2		39	5
	Ng and MacGregor (2012)		7	O (MET)	22	41	27		14		27	5
	Ng and MacGregor (2012)		7	O (MOR)	73	38	33		1		51	5
	Ng and MacGregor (2012)		7	SD	129	58	23		12		24	5
	Ng and MacGregor (2012)		7	ST	25	68	28		0		12	4

(*continued on next page*)

Table 2 (*continued*)

	Author (Year)	Target population	Quality score	Drug class	Sample size (n)	Source						
						Friend or family (free)[a] (%)	Friend or family (buy) (%)	Legitimate medical source (%)	Illegitimate medical source[c] (%)	Internet (%)	Dealer or street market (%)	Theft[b] (%)
26	Nielsen et al. (2013)	PWUD (Pharmaceuticals, in treatment)	9	O	108	30	39	31	12		46	4
	Nielsen et al. (2013)		9	SD	144	44	19	72	22		17	6
27	Novak et al. (2007)	General population (Adults)	13	ST	86	66	13		20	5		35
28	Novak et al. (2016)	General population (Adolescents, adults)	12	OP	949	44	13		16	4		27
	Novak et al. (2016)		12	SD	1099	61	7		19	3		16
	Novak et al. (2016)		12	ST	498	47	14		23	8		27
29	O'Reilly et al. (2007)	PWUD (Injecting, in treatment)	7	O	101	37	39	25	1		24	2
	O'Reilly et al. (2007)		7	SD	101	26	22	9	8		11	1
30	Ross et al. (1996)	PWUD (Opioids or heroin, in and out of treatment)	10	SD	210			47				
31	Schepis and Krishnan-Sarin (2009)	General population (Adolescents)	13	O	2589	47	9	20	3	0	5	10
	Schepis and Krishnan-Sarin (2009)		13	SD	148	33	6	20	2	0	7	9
	Schepis and Krishnan-Sarin (2009)		13	ST	740	50	12	11	2	2	7	11
32	Schulte et al. (2016)	PWUD (Opioids, in and out of treatment)	12	O	177	53					81	
33	Smith et al. (2007)	PWUD (Injecting, in treatment)	7	O	98	63		62	6			3
	Smith et al. (2007)		7	SD	102	87	27	80	13			8
34	Vivian et al. (2005)	PWUD (Other than alcohol or marijuana, out of treatment)	10	O	52						58	
Number of studies for meta-analysis						30	24	21	29	13	25	19

Quality assessment based on an adaptation of the tool developed by DuRant (1994) (see Appendix B). Maximum score = 14.

PWUD = People who use drugs, O = Opioids, SD = Sedatives, ST = Stimulants, BP = Buprenorphine, MET = Methadone, MOR = Morphine, OXY = Oxycodone.

[a] Includes studies that indicated drugs were sourced from friends or family, but did not specify whether money was exchanged.

[b] Includes theft from family, friends and others.

[c] Includes faking symptoms, doctor shopping and prescription forgery practices.

[d] Indicates partial agonist opioids (i.e. buprenorphine, buprenorphine-naloxone) Source categories are not mutually exclusive.

Table 3
Results of source meta-analyses (random effects model).

	Prevalence (%)	LCI (95%)	HCI (95%)	Cochran's Q	I^2	Tau^2	No. of studies	No. of estimates	Total sample size
Friend or family (free)	57	53	62	2947.87	98.51	0.08	30	45	39,889
Dealer or street market	32	23	41	19335.68	99.80	0.38	25	39	65,661
Legitimate medical source	29	23	36	7830.83	97.35	0.16	21	32	64,592
Friend or family (buy)	23	18	29	1556.83	98.52	0.11	13	24	16,457
Theft	10	8	12	1403.28	97.65	0.04	19	34	35,727
Illegitimate medical source	7	6	10	1057.94	97.35	0.04	16	29	31,829
Internet	2	1	3	325.19	93.54	0.01	13	22	33,530

Source categories are not mutually exclusive. Studies included in each meta-analysis are listed in Table 2.

on sample size or method (4) and reporting the views of HCPs (1).

Using the 34 (34.7%) comparable studies, individual meta-analyses were performed for the following seven source types: friends or family (free), friends or family (purchase), dealer or street market, legitimate medical source, illegitimate medical source, Internet and theft. The results indicate that pharmaceutical drugs are most commonly sourced for NMU from friends or family for free and least commonly via the Internet (Table 3).

The influence of individual studies on the overall prevalence estimate for each source was explored by serially excluding each study in a sensitivity analysis. There were no studies that influenced the overall prevalence estimates by more than 3% (Appendix F).

In these meta-analyses, there was a high level of heterogeneity as indicated by an I-squared of greater than 90%. Potential influences on prevalence estimates were investigated using subgroup analysis for date of publication, study quality, target population and drug class. There was minimal variation in the prevalence estimates for studies published between 2003 and 2009 compared with 2010 and 2017, and heterogeneity remained high. Likewise, patterns of sourcing were similar for the high and moderate quality studies, with heterogeneity slightly reduced but still high (see Appendix G of the Supplementary Materials).

There were some differences in patterns of sourcing when analyzed by target population and drug class (Fig. 2).

3.3.1. Non-medical sourcing

3.3.1.1. Friends and family. The meta-analyses revealed that friends and family are the most prominent source of pharmaceutical drugs for NMU across all populations and drug classes (Fig. 2). More often pharmaceutical drugs are obtained for free from friends or family than they are purchased. Friends and family may be a preferred access point for convenience and because the scrutiny of HCPs can be avoided (Anglin and White, 1999).

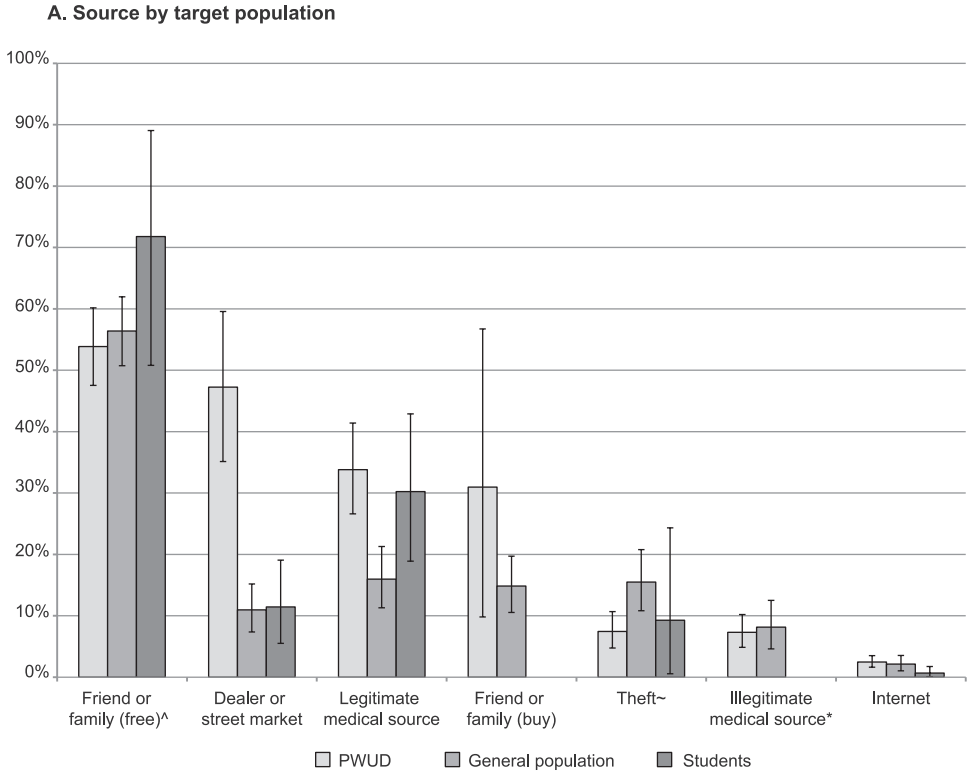
The majority of PWUD reported accessing pharmaceutical drugs for NMU from friends and family without payment (54%, 95% CI 48%–60%). It is well known that PWUD regularly socialize with other users with ready access to medications through Opioid Substitution Therapy (OST) and other treatment services (Bruno, 2007; Carise et al., 2007; Duffy and Baldwin, 2012; Fountain et al., 2000; Furst, 2014; Johanson et al., 2012; Mitchell et al., 2009; Nielsen et al., 2008; Vivian et al., 2005; Winstock and Lea, 2010; Winstock et al., 2008). Within these communities, informal medication sharing occurs and is often driven by altruistic motives or the desire to help another who may be experiencing the effects of withdrawal (Allen and Harocopos, 2016; Duffy and Baldwin, 2012; Johnson and Richert, 2015b; Kaye et al., 2014). More formal relationships involving the exchange of pharmaceutical drugs for money, other medications or illicit drugs may also take place between PWUD. One study found that these types of relationships were established to accommodate a regular or ongoing supply rather than occasional offerings (Johnson and Richert, 2015b). Australian research has shown that when pharmaceutical opioids or sedatives are purchased by PWUD for NMU, they are more often purchased from friends or family than acquaintances or dealers (Stafford and Breen, 2016, 2017; Stafford and Burns, 2010, 2011, 2012, 2013, 2014, 2015).

Almost three-quarters of students reported accessing pharmaceutical drugs for NMU from friends or family for free (72%, 95% CI 51%–89%). This review found that stimulants used for the treatment of attention deficit hyperactivity disorder (ADHD) are often sourced from peers with prescriptions (Barrett et al., 2005; DeSantis et al., 2010; DeSantis et al., 2008; Dupont et al., 2008; McCabe et al., 2006c; Vosburg et al., 2016). The excess supply of medications from patients not taking their required dosage facilitates sharing with other students, who then use the drugs as study aids or for recreational purposes (DeSantis et al., 2010; DeSantis et al., 2008; Vrecko, 2015). Parents are also a meaningful source of pharmaceutical drugs for students, particularly for opioids and sedatives (DeSantis et al., 2009; DeSantis et al., 2008; Dupont et al., 2008; Holloway and Bennett, 2012; McCabe et al., 2007; Schepis and Krishnan-Sarin, 2009). One study found that students who source opioids from parents were less likely to use the drugs recreationally (McCabe et al., 2007).

General population surveys have also showed a high prevalence of sourcing through friends and family (56%, 95% CI 51%–62%). The Australian National Drug Strategy Household Survey found that friends and family are consistently reported as the usual source of sedatives for NMU in the past year (AIHW, 2001, 2004, 2007). Stimulant drugs are overwhelmingly accessed through social networks (Cassidy et al., 2015a,b; Vuolo et al., 2014) and one study found that those sourcing stimulants from friends or family have a lower prevalence of NMU than those sourcing from dealers (Chen et al., 2014).

3.3.1.2. Dealers. The meta-analyses showed that access to pharmaceutical drugs for NMU via dealers is relatively common for PWUD (47%, 95% CI 35%–60%) and more so than for the general population (11%, 95% CI 7%–15%) and students (11%, 95% CI 6%–19%) (Fig. 2). Some research has found that often people who illegally sell pharmaceuticals also sell illicit drugs (Rigg et al., 2012; Vuolo et al., 2014) and in circumstances where dealers sell pharmaceutical drugs alone, they will often be present in illicit drug scenes (Firestone and Fischer, 2008; Fischer et al., 2009). Given that PWUD are likely to have regular contact with street-based drug markets as part of their own drug use, it is understandable that pharmaceutical drugs are also sourced in this way (Chan et al., 2016; Lankenau et al., 2007; Schulte et al., 2016). Moreover, it is well known that PWUD may substitute illicit drugs such as heroin for pharmaceutical drugs depending on availability, which may explain their contact with both markets (Bruno, 2007; Smith et al., 2007).

As with illicit drugs, the pricing of pharmaceutical drugs varies according to supply and availability within the market (Sajan et al., 1998). The specific black market prices reported in the included studies varied depending on the drug or brand name under investigation and the dosage amount (Bazazi et al., 2011; Elwood, 2001; Furst, 2014; Inciardi et al., 2009a; Monte et al., 2009; Sajan et al., 1998; Winstock and Lea, 2010). Pharmaceutical drugs sold on the black market are reportedly more expensive than those available through medical sources (Bachhuber and Cunningham, 2013; Bazazi et al., 2011; Sajan et al., 1998), indicating that persons sourcing from dealers may be



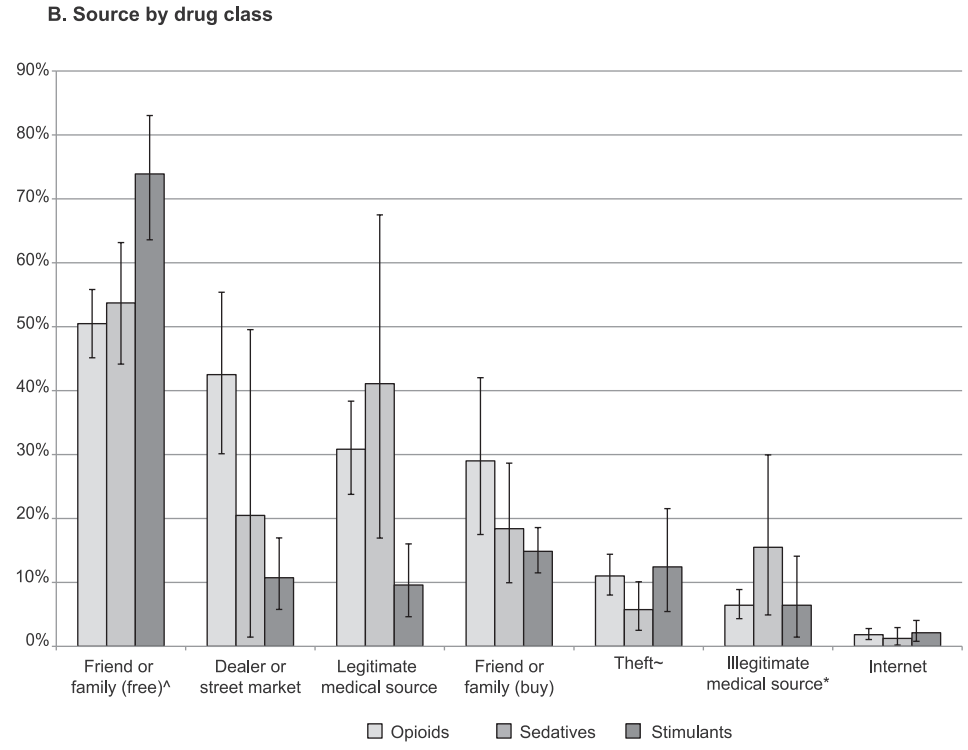


Fig. 2. Source of pharmaceutical drugs for NMU by target population and drug class – Meta-analyses results.
A. Subgroup analysis by target population: Excludes one study by Ng and MacGregor (2012) that sampled a police detainee population. There were no studies that estimated the prevalence of sourcing by students through friends or family (buy) and illegitimate medical.
B. Subgroup analysis by drug class: Appendix G provides prevalence estimates for sourcing opioids excluding medications commonly used in pharmacotherapy treatment (i.e. buprenorphine, buprenorphine-naloxone, methadone).
See Appendix G for complete meta-analyses results.
^ Includes studies that indicated drugs were sourced from friends or family, but did not specify whether money was exchanged.
~ Includes theft from family, friends and others.
*Includes faking symptoms, doctor shopping and prescription forgery practices.

motivated to do so for reasons other than cost. There also may be pricing differences depending on the purchaser. For instance, one study found that people who inject drugs typically paid higher prices for black market buprenorphine than those who do not inject drugs (Bazazi et al., 2011).

3.3.1.3. Internet. Despite the apparent availability of pharmaceutical drugs online (Schepis et al., 2008; The National Center on Addiction and Substance Abuse (CASA), 2004, 2008), the meta-analyses revealed that sourcing via the Internet is uncommon across all populations and drug classes (less than 3% for all groups; Fig. 2) (Apantaku-Olajide and Smyth, 2013; Bachhuber and Cunningham, 2013; Dasgupta et al., 2013;

Festinger et al., 2016; Forman et al., 2006; Frauger et al., 2012; Inciardi et al., 2010; Littlejohn et al., 2005; Martins et al., 2009; McGregor et al., 2011; Novak et al., 2016; Schepis and Krishnan-Sarin, 2009; Van Buskirk et al., 2013). A study of public web-forum discussions found that the Internet may be used as a backup for sourcing morphine during periods of withdrawal or when unable to access a pharmacy (Van Hout and Hearne, 2016). Six studies in the review identified that there may be several factors dis-incentivizing the sourcing of drugs online including risk of detection and seizure by customs, shipping delays and costs, and the risk of purchasing counterfeit products (Bachhuber and Cunningham, 2013; Cicero et al., 2008; Fischer et al., 2010; Inciardi et al., 2007a; Nielsen and Barratt, 2009; Van Hout and Hearne, 2016).

3.3.2. Medical sourcing

The meta-analyses showed that the medical system is a key access point for pharmaceutical drugs for NMU. Overall, sourcing via legitimate prescriptions is more common (29%, 95% CI 23%–36%) than sourcing illegitimately through practices such as faking symptoms, doctor shopping and prescription forgery (7%, 95% CI 6%–10%; Table 3).

3.3.2.1. Legitimate medical sourcing. The meta-analyses found that accessing pharmaceutical drugs via legitimate medical sources is particularly common among PWUD (34%, 95% CI 27%–1%). In an Australian sample of drug treatment clients, Nielsen et al. (2013) found that presenting to a HCP with a real symptom was the usual access point for benzodiazepines. This may reflect the regular contact that PWUD have with the medical system due to health issues or as part of formal treatment. Among PWUD, those with ready access to the medical system through health insurance are more likely to use medical than non-medical sources (Cicero et al., 2008; Ibañez et al., 2013).

When pharmaceutical drugs are accessed legitimately from the medical system, drugs are initially obtained for real symptoms, illness or injury (Harocopos and Allen, 2015). This suggests that the excess supply of medications may contribute to their misuse and diversion (Buykx et al., 2010; Inciardi et al., 2007a; Lewis et al., 2014; McCabe et al., 2013). Research has shown that medical sourcing is prominent among females (Cicero et al., 2011; Cicero et al., 2008; White et al., 2016a). The medical system may be a preferred access point because it is legal, lower in cost and potentially safer (Bouland et al., 2015; Ronka and Katainen, 2017).

3.3.2.2. Illegitimate medical sourcing.. The meta-analyses indicated that illegitimately sourcing pharmaceutical drugs through the medical system by faking symptoms, prescription forgery or doctor shopping is relatively uncommon among the general population (8%, 95% CI 5%–13%) and PWUD (7%, 95% CI 5%–10%), as well as for opioids (6%, 95% CI 4%–9%), sedatives (15%, 95% CI 5%–30%) and stimulants (6%, 95% CI 1%–14%; Fig. 2). It is possible that the elevated risks associated with deceiving practitioners act as a deterrent, particularly in the context of Prescription Monitoring Programs (PMP) that have proliferated in countries such as the US in recent years (Gabay, 2015). In fact, research has shown that successfully diverting drugs through these practices requires considerable time and effort in order to gather medical knowledge, identify the most amenable practitioners to target, develop a particular profile or appearance, and build rapport with practitioners (Ronka and Katainen, 2017; Van Hout and Hearne, 2016; Worley and Thomas, 2014).

Contrary to the meta-analyses results, the review found that HCPs perceive doctor shopping to be widespread (Inciardi and Cicero, 2009; Smith et al., 2007; The National Center on Addiction and Substance Abuse (CASA), 2005). Patient behaviors such as making direct and specific requests for medications, becoming forceful and bullying the prescriber are perceived to be common indicators of doctor shopping (Leukefeld et al., 2007; Novak et al., 2007; Worley et al., 2015). On the other hand, it has also been acknowledged that potential drug diversion by patients (Larance et al., 2011c) and prescription forgery in particular, can be difficult for practitioners to identify (Boeuf and Lapeyre Mestre, 2007), especially in countries with fewer regulations and incomplete patient records (Lapeyre-Mestre et al., 2014).

Seven cohort studies were identified that examined the prevalence of doctor shopping in large patient samples (Cepeda et al., 2014; Chenaf et al., 2016; Chilcoat et al., 2016; Delorme et al., 2016; Han et al., 2014; Morris et al., 2014; Simeone, 2017). Different definitions of doctor shopping were adopted in these studies, so no attempt has been made here to synthesize the estimates produced. Overall, the prevalence of doctor shopping was low − 0.17% for opioids in a US sample (Simeone, 2017) and 7.2% in a French sample (Pauly et al., 2012), 0.12% for oxycodone (Chilcoat et al., 2016), 4.0% for codeine by chronic non-cancer pain patients (Chenaf et al., 2016), 8.4% for high-dosage buprenorphine (Delorme et al., 2016), 4.5% for stimulant ADHD medications (Cepeda et al., 2014) and 1.9% for benzodiazepines (Pauly et al., 2012).

The other method of illegitimate medical sourcing that was explored in the literature involves HCPs sourcing drugs for NMU directly from their workplace for their own use. In this setting, diversion occurs through a number of strategies, including substitution or defrauding of patients, prescription forgery and manipulation, and the misuse and theft of medication samples and expired drugs (Cummings et al., 2011; Inciardi et al., 2006; Merlo et al., 2014). The overt presence of pharmaceuticals in the workplace of HCPs facilitates their ease of diversion in this context (Merlo et al., 2014).

3.4. Diversion of pharmaceutical drugs for NMU

The review identified 65 studies that examined diversion. Of these, 24 (36.9%) surveyed different population groups about their involvement in gifting, selling or trading pharmaceutical drugs. The results of these individual studies are presented in Table 4.

Due to variations in the drug classes and target populations examined and the time scales adopted, only seven (29.2%) of these studies contained comparable data for meta-analysis. This comprised four studies that estimated the prevalence of opioid diversion by PWUD in the past three months (Duffy and Baldwin, 2012; Johnson and Richert, 2015a; Launonen et al., 2015; Nielsen et al., 2008) and three studies that estimated the lifetime prevalence of stimulant diversion by students (Darredeau et al., 2007; DeSantis et al., 2013; Gallucci et al., 2015). For these studies, individual random-effects meta-analyses were performed for each diversion mechanism and the results indicate that gifting may be more common than selling and trading for both groups (Table 5).

The literature suggests that PWUD may be motivated to sell or trade pharmaceutical drugs to support their own drug use (Furst, 2014; Inciardi et al., 2009a; Johnson and Richert, 2015b). Pharmaceutical drugs are a valuable commodity among communities of PWUD, particularly in circumstances where others may be experiencing the effects of withdrawal or do not have access to treatment services (Allen and Harocopos, 2016; Duffy and Baldwin, 2012; Johnson and Richert, 2015b; Kaye et al., 2014). In prison environments, pharmaceutical drugs may be traded for other drugs, tobacco or toiletries (Tompkins et al., 2009).

To varying degrees, research has documented the diversion of supervised OST doses such as methadone whereby clients have removed all or part of their dose at the time of administration (Larance et al., 2011a,c; Tompkins et al., 2009; Winstock et al., 2009a,b). While, often, such diversion may be for the purpose of saving for later personal use (Larance et al., 2011a), it has also been documented that others may coerce treatment clients to share or on-sell their doses (Allen and Harocopos, 2016; Bruno, 2007; Green et al., 2013). Such coercion has also been widely reported in prison-based treatment settings (Havnes

Table 4
Prevalence of pharmaceutical diversion by gifting, selling or trading.

	Author (Year)	Population	Quality score	Drug class	Sample size (n)	Gifting (%)	Selling (%)	Trading (%)	Combined (%)	Combined inclusions	Time scale
1	Aldridge et al. (2011)	Patients (ADHD)	11	ST	513				17	Gift, sell	30 days
2	Ashrafioun et al. (2014)	Patients (Dental)	12	O	338	5	2	1	7	Gift, sell, trade	12 months
3	Belcher et al. (2014)	Patients (Non-cancer pain)	10	O	952	4	0		4	Offer, supply, sell	Lifetime
4	Cottler et al. (2013)	General population (Adolescents)	11	ST	11,048	5	3	2	7	Gift, sell, trade	Lifetime
5	Darredeau et al. (2007)[b]	Patients (ADHD)	11	ST	66	42	8		44	Gift, sell	Lifetime
6	Davis and Johnson (2008)	PWUD (Heroin, not from treatment)	8	O	586		40				Lifetime
7	DeSantis et al. (2013)[b]	Patients (ADHD) Students (University)	10	ST	120	53	39				Lifetime
8	Duffy and Baldwin (2012)	PWUD (Methadone, from treatment)	9	O (MET)	854	13	5	3			12 months
	Duffy and Baldwin (2012)[a]	PWUD (Methadone, from treatment)	9	O (MET)	854	4	2	1			4 weeks
9	Gallucci et al. (2015)	Patients (Stimulant holders) Students (University)	12	ST	151				59	Gift, sell	Lifetime
	Gallucci et al. (2015)[b]	Patients (Stimulant holders) Students (University)	12	ST	151	31			32	Gift, sell	30 days
10	Goldsworthy et al. (2008)	General population (Adolescents, adults)	10	G	700	23					Lifetime
11	Holloway and Bennett (2012)	Students (University)	8	G	1517	10	1	1	11	Gift, sell, trade	Lifetime
	Holloway and Bennett (2012)	University staff	8	G	458	10	< 1	< 1	10	Gift, sell, trade	Lifetime
12	Holloway et al. (2013)	Students (University)	8	G	437	16	1	1			Lifetime
13	Johnson and Richert (2015a)[a]	PWUD (OST, from treatment)	12	O (BP, MET)[c]	411	16	14	3	24	Gift, sell, trade	30 days
	Johnson and Richert (2015a)	PWUD (OST, from treatment)	12	O (BP, MET)[c]	411				9	Gift, sell, trade	Lifetime
14	Kaye et al. (2014)	PWUD (Psycho-stimulants, from treatment and not from treatment)	11	ST	19				47	Gift, sell	Lifetime
15	Larance et al. (2011a)	PWUD (OST, from treatment)	11	O (BP, BNX, MET)[c]	424				28	Gift, sell	6 months
16	Lasopa et al. (2015)	General population (Youth)	13	ST	738	27	19	17			Lifetime
17	Launonen et al. (2015)	PWUD (OST, from treatment)	10	O (BNX, MET)[c]	1452		4				> 6 months ago
	Launonen et al. (2015)[a]	PWUD (OST, from treatment)	10	O (BNX, MET)[c]	1452		3				< 6 months ago
	Launonen et al. (2015)[a]	PWUD (OST, from treatment)	10	O (BNX, MET)[c]	1391	8					> 6 months ago
	Launonen et al. (2015)	PWUD (OST, from treatment)	10	O (BNX, MET)[c]	1391	5					< 6 months ago
18	Nielsen et al. (2008)[a]	PWUD (injecting, from treatment)	9	O	232	37	12	21			30 days
19	Poulin (2007)	Students (Secondary)	14	ST	264	24	19				30 days
20	Poulin (2001)	Students (Secondary)	14	ST	710	15	7				12 months
21	Rabiner et al. (2009)	Students (University)	10	ST	115				26	Gift, sell	6 months
22	Ross et al. (1996)	PWUD (OST, from treatment and heroin, not from treatment)	10	SD	210				58	Gift, sell	6 months
23	Vuolo et al. (2014)	PWUD (Pharmaceuticals, not from treatment)	12	G	404		11				3 months
24	Wilens et al. (2006)	Patients (ADHD, adolescents, young adults)	10	G	55		11				Lifetime

Includes studies that estimated the prevalence of actual diversion, as opposed to practices where persons were 'approached' or 'asked' to divert. Diversion categories are not mutually exclusive. Quality assessment based on an adaptation of the tool developed by DuRant (1994) (Appendix B). Maximum score = 14.

PWUD = People who use drugs, O = Opioids, SD = Sedatives, ST = Stimulants, G = General, BP = Buprenorphine, BNX = Buprenorphine-naloxone, MET = Methadone.

[a] Denotes studies that were included in the meta-analyses for diversion of opioids by PWUD.

[b] Denotes studies that were included in the meta-analyses for diversion of stimulants by students.

[c] Indicates studies that included partial opioid agonists (i.e. buprenorphine, buprenorphine-naloxone).

Table 5
Results of diversion meta-analyses (random effects model).

	Prevalence (%)	LCI (95%)	HCI (95%)	Cochran's Q	I^2	Tau^2	No. of studies	No. of estimates	Total sample size
Opioids by PWUD (past 3 months)									
Gift	12	3	25	207.34	98.55	0.11	4	4	2888
Sell	6	1	12	99.95	96.97	0.05	4	4	2949
Trade	6	0	18	102.08	98.04	0.12	3	3	1497
Stimulants by students (lifetime)									
Gift	52	44	60	4.63	56.81	0.01	3	3	337
Sell	25	9	45	27.82	92.81	0.12	3	3	337

et al., 2013; White et al., 2016b).

The relatively high prevalence of lifetime stimulant diversion by students may reflect the availability of surplus medications, as well as increased peer pressure in student environments (DeSantis et al., 2013; Gallucci et al., 2015). Gallucci et al. (2015) found that when money was exchanged between students, in 46.1% of reports it was for the financial gain of the supplier, but may also occur as a gesture of goodwill (38.5%) and to cover the costs of the medication (7.6%).

Among patient samples, results from the individual studies suggest that stimulants are more likely to be given away, sold or traded than opioids (Ashrafioun et al., 2014; Belcher et al., 2014; Darredeau et al., 2007; DeSantis et al., 2013; Wilens et al., 2006). Research has shown that a minority of patients appropriately disposes of leftover medications, which may facilitate their diversion (Inciardi et al., 2007a; Lewis et al., 2014).

3.4.1. Risk factors for diversion

This review identified a substantial evidence base examining the risk factors for diversion among various populations.

For PWUD, risk factors include the injection of illicit and pharmaceutical drugs (Launonen et al., 2015; Winstock and Lea, 2010; Winstock et al., 2008), lower treatment satisfaction (Johnson and Richert, 2015a,c), higher on average alcohol consumption (Johnson and Richert, 2015b), and consumption of a lower dosage of medication (irrespective of the prescribed amount) (Johnson and Richert, 2015b; Launonen et al., 2015).

For students, previous NMU was most commonly found to be associated with diversion (DeSantis et al., 2013; Gallucci et al., 2015; McCabe et al., 2014; Poulin, 2001; Rabiner et al., 2009; Stogner et al., 2014), followed by sorority/fraternity membership (in university populations) (DeSantis et al., 2013; DeSantis et al., 2008; Stogner et al., 2014) and being a current prescription holder (Boyd et al., 2007; McCabe et al., 2006b). In a sample of high school students, females and students without college plans were more likely to be approached to divert their medications (McCabe et al., 2004). Other less commonly identified risk factors were the use of alcohol and other illicit drugs (DeSantis et al., 2013), association with non-medical using peers (DeSantis et al., 2013), lower incomes and unemployment (Stogner et al., 2014).

Finally, patients with a greater supply of medication (Belcher et al., 2014), those engaged in NMU (Ashrafioun et al., 2014; Darredeau et al., 2007; DeSantis et al., 2013; Gallucci et al., 2015) and more aberrant or 'off-label' medication behaviors (Belcher et al., 2014; DeSantis et al., 2013) are reportedly more likely to participate in diversion. Substance use disorders were also positively associated with diversion among patient groups (Walker and Webster, 2012; Wilens et al., 2006).

3.4.2. Organized criminal involvement

The literature indicates that, while a black market for pharmaceutical drugs exists, it operates at the lowest level of distribution and there is little to no organized crime or involvement by criminal gangs or networks (Allen and Harocopos, 2016; Fountain et al., 2000; O'Reilly et al., 2007; Smith et al., 2007; Vuolo et al., 2014; Yearwood, 2012). That said, coordinated operations have been uncovered in the US involving 'pill brokers' who proactively develop relationships with patients and the elderly to assist them to fill their prescriptions (Green et al., 2013; Inciardi et al., 2009a; Inciardi et al., 2007a; Rigg et al., 2010; Worley and Thomas, 2014). The brokers buy the medications from the patients for a considerably lower cost than the black market price and then work directly with users to distribute them (Inciardi et al., 2009a; Rigg et al., 2012; Rigg et al., 2010). In the US, drug tourism involving American citizens travelling to Mexico, South America and the Caribbean for pharmaceutical supplies has also been uncovered (Elwood, 2001; Inciardi et al., 2007a; Valdez and Sifaneck, 1997).

4. Discussion

To our knowledge, this is the first review to consolidate what is known about the source and diversion of pharmaceutical opioids, sedatives and stimulants for NMU in Australia, Canada, Europe, the UK and the US. This is a topic of increasing importance, as international data indicate that the misuse problem is escalating, along with associated health and economic consequences including mortality (UNODC, 2017). An understanding of source and diversion is critical for developing effective prevention and treatment interventions (Ritter, 2005).

This review identified a large evidence base examining the source of pharmaceutical drugs for NMU. From this literature, it is clear that friends and family are the most prominent source reported by populations of non-medical users. Moreover, giving medications away for free is the most commonly reported diversion mechanism. Together, these findings confirm that medication sharing is common and widely perceived to be socially acceptable (Beyene et al., 2013; Goldsworthy et al., 2008). These informal exchanges are reminiscent of the 'social supply' of illicit drugs, which has been described in the broader literature (see, for example, Grigg et al. (2015), Hough et al. (2003) and Coomber et al. (2016)). Social supply is based upon friendships and commonly occurs in closed settings, rather than in street-based drugs markets involving dealers (Grigg et al., 2015).

There are several factors that may contribute to the social supply of pharmaceutical drugs. First, few patients report receiving information from their treating practitioners about appropriate storage and disposal practices for leftover medications (Kennedy-Hendricks et al., 2016) and consequently, patients regularly retain surplus medications that then become susceptible to misuse and diversion (Daniulaityte et al., 2014; Lewis et al., 2014; McCabe et al., 2013). Second, people may not be aware of the risks associated with diversion and NMU (Johnston et al., 2015; U.S. Food and Drug Administration (FDA), 2015). Potential risks may be mitigated due to the routine prescription of controlled medications, the purity of pharmaceutical drugs compared with illicit drugs and the reduced legal risks associated with supply and possession (Topp, 2006). There may be a lack of information provided by HCPs on the potential risks of diversion (Kennedy-Hendricks et al., 2016). In fact, the challenges in communicating such risks to patients have been acknowledged by practitioners themselves (Chen et al., 2014; Childers and Arnold, 2012).

The extant literature provides a comprehensive profile of people involved in diversion. Individuals who gift, sell or trade pharmaceutical

drugs tend to endorse or participate in NMU. For PWUD and patients, those involved in diversion exhibit less compliant medication behaviors and tend to be more vulnerable in terms of substance use and social disadvantage. In American student populations, affiliation with 'Greek' societies elevates the risk of diversion, which is unsurprising given the strength of social networks in these types of groups. These findings may be used to inform risk assessment processes, which is likely to be valuable given that research has shown that some practitioners face difficulties in identifying patients at risk of diversion (Larance et al., 2011c).

Despite the prominence of social supply, policies to date have largely focused on reducing access to pharmaceutical drugs for NMU from the medical system via practices such as doctor shopping. For example, PMPs have been implemented widely throughout the US (Gabay, 2015) and plans for the roll-out of real-time prescription monitoring are underway in Australia (State Government of Victoria, 2017). While such programs may have important deterrent effects, this review has found that sourcing pharmaceutical drugs for NMU illegitimately via the medical system is relatively uncommon. In fact, an important US study that linked medical and PMP records found that a majority of persons in the study who died from methadone-related overdoses were not flagged in the PMP prior to death (Weimer et al., 2011), which echoes the findings of another recent study (Hawk et al., 2017). In order to reduce the risks of pharmaceutical NMU, including mortality, it is pertinent that practitioners and policy makers turn their attention to developing strategies for addressing the social supply of pharmaceutical drugs.

This review also found that the dealing and trading of pharmaceutical drugs occurs and street-based drug markets are a particularly common access point for PWUD. The black market for pharmaceutical drugs is a potentially lucrative industry, with black market prices typically a lot higher than those in the legitimate market (Bachhuber and Cunningham, 2013; Bazazi et al., 2011; Elwood, 2001; Sajan et al., 1998; Winstock et al., 2009a). Pharmaceutical drugs are valuable commodities and particularly so in communities where people are experiencing the effects of withdrawal and may have inadequate access to treatment services (Allen and Harocopos, 2016; Duffy and Baldwin, 2012; Johnson and Richert, 2015b; Kaye et al., 2014). Evidence to date suggests that the pharmaceutical black market is dominated by small-scale dealers rather than organized criminal networks or gangs (Fountain et al., 2000; O'Reilly et al., 2007; Smith et al., 2007; Yearwood, 2012), though it will be important to continue to monitor this over time particularly as 'pill brokerage' and sponsorship arrangements have emerged in parts of the US (Green et al., 2013; Inciardi et al., 2009a; Inciardi et al., 2007a; Rigg et al., 2010; Worley and Thomas, 2014).

It is relevant to acknowledge the variable risks and harms associated with the misuse and diversion of different types of pharmaceutical drugs. There is evidence that opioids used in pharmacotherapy treatment such as methadone and buprenorphine are subject to misuse and diversion, with motivations ranging from the pursuit of euphoria, insufficient dosing, affordability, withdrawal management and in substitute of other drugs (Allen and Harocopos, 2016; Bazazi et al., 2011; Yokell et al., 2011). However, the highly regulated environment in which these drugs are prescribed for pharmacotherapy treatment (such as the use of supervised dosing) means that their diversion occurs infrequently and tends to involve only single doses (Johnson and Richert, 2015a; Larance et al., 2011a; Launonen et al., 2015; Winstock et al., 2008) and overall their use is associated with a substantial reduction in mortality risk (Sordo et al., 2017). It is when methadone is prescribed for pain that it is overrepresented in overdose deaths (Kuehn, 2012), which is likely to reflect the more flexible regulatory environment and thus, the elevated risk of diversion with limited oversight of take-home medication. Importantly, the NMU of opioids not used in treatment such as oxycodone and fentanyl are more commonly attributed to the rise in overdose deaths (UNODC, 2017).

It has been acknowledged elsewhere that our understanding of pharmaceutical drug diversion reflects only the answers provided by the people whom we have asked (Inciardi and Cicero, 2009; Inciardi et al., 2009b). Indeed, this review has clearly demonstrated that research to date has overwhelmingly focused on populations of end-users and, from these studies, we consistently conclude that supply is largely driven by informal exchanges between persons known to one another. However, it is possible that other sourcing routes such as doctor shopping and online purchasing are more prevalent among pharmaceutical dealers who obtain the drugs for the purpose of distributing to others (Festinger et al., 2016; Inciardi et al., 2009b; Inciardi et al., 2010). It will be important for future research to seek better understanding of the source of pharmaceutical drugs for those involved in supplying them, as this will contribute to a more complete understanding of the supply chain.

The broad scope of this review may be both a strength and limitation of the approach. It is a strength because, to our knowledge, this is the first review to consolidate the evidence base from Australia, Canada, Europe, the US and the UK regarding the source and diversion of opioids, sedatives and stimulants for NMU. However, the broadness of the search strategy may have resulted in the inadvertent omission of key literature relating to specific source types or diversion mechanisms. Literature from non-English speaking European countries are likely to have been underrepresented in this review due to the restriction of records to English, which has potentially limited our ability to comment on pharmaceutical sourcing and diversion in these countries. Regarding the meta-analyses, the data were derived from studies that used different survey instruments, which limited our ability to precisely estimate the prevalence of pharmaceutical sourcing and diversion.

4.1. Conclusion

Despite the current policy focus on reducing access to pharmaceutical drugs via the medical system, this review finds that pharmaceutical opioids, sedatives and stimulants for NMU are primarily sourced through informal exchanges between friends and family, while doctor shopping and prescription forgery are relatively uncommon. Policy efforts should be targeted towards addressing the social supply of pharmaceutical drugs and people at particular risk of diversion, including patients displaying aberrant medication behaviors, people with substance use issues and students in fraternity/sorority environments. It will be important to continue monitoring the pharmaceutical black market, which is a lucrative industry, particularly among communities of PWUD. Future research should seek to better understand sourcing and diversion from the perspective of those involved in supplying pharmaceutical drugs for NMU.

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Contributors

SH, DB and SN designed the study and provided input on the original research plan. SH managed the literature searches, summarized and coded the literature, conducted the meta-analyses and wrote the first draft of the manuscript. SN oversaw the review conduct and provided detailed comments on methodology and each version of the

manuscript. DB provided input on an early version of the manuscript. All authors have contributed to and approved the final manuscript.

Conflict of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2018.02.010.

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