Title: Harmonizing post-market surveillance of prescription drug misuse: A systematic review of observational studies using routinely collected data (2000–2013).

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Abstract

Background Prescription drug misuse is a growing public health concern globally. Routinely collected data provides a valuable tool for quantifying prescription drug misuse.

Objective To synthesize the global literature investigating prescription drug misuse utilizing routinely collected, person-level prescription/dispensing data to examine reported measures, documented extent of misuse and associated factors.

Methods We searched MEDLINE, Embase, CINAHL, MEDLINE In Process, Scopus citations and Google Scholar for relevant articles published between January 1 2000-July 31 2013. We screened 10,803 abstracts and retrieved 281 full-text manuscripts. Fifty-two peer-reviewed, English-language manuscripts met our inclusion criteria: an aim/method investigating prescription drug misuse and a measure of misuse derived exclusively from prescription/dispensing data.

Results Four proxies of prescription drug misuse were used commonly across studies: number of prescribers, dispensing pharmacies, early refills and volume of drugs dispensed. We identified 89 unique measures of misuse across the 52 studies, reflecting the heterogeneity in how measures are constructed; single or composite; different thresholds, cohort definitions and time period of assessment. Consequently, it was not possible to make definitive comparisons about the extent (range reported: 0.01-93.5%), variations and factors associated with prescription drug misuse.

Conclusion Routine data collections are relatively consistent across jurisdictions. Despite the heterogeneity of the current literature, our review identifies the capacity to develop universally accepted metrics of misuse applied to a core set of variables in prescription/dispensing claims. Our timely recommendations have the potential to unify the global research field and increase the capacity for routine surveillance of prescription drug misuse.

Key points

- Prescription drug misuse is increasing globally. This can be monitored readily using routinely collected data; quantifying drug access patterns at the population-level.
- Our review identified only four common proxies for prescription drug misuse (number of prescribers; number of dispensing pharmacies; volume of drug(s) dispensed; and/or overlapping prescriptions/early refills) yet they were used to derive 89 unique definitions of misuse due to variations in thresholds, or use alone or in combination.
- We recommend the development of consistent and replicable metrics to facilitate monitoring and comparisons of the extent of prescription drug misuse across health care settings and over time.

1 Introduction

Research demonstrates a high degree of variability in how drugs are prescribed and used [1]. Drugs including sedatives, anxiolytics, analgesics and stimulants are often taken excessively to enhance desired effects [1]. The consequences of excessive use are a major public health concern and include drug tolerance [2, 3], increased risk of side effects [3-5], overdose [6], dependence [7], hospitalization [5] or death [2, 8, 9]. These risks are escalated with concominant prescription drug, alcohol or illicit drug use [10-16].

Research methodologies including medical chart [17], surveys [18], qualitative [19, 20] and observational studies [21] have been used to explore prescription drug misuse. In recent decades, the growing availability of routinely collected health information has increased opportunities to undertake population-based surveillance of prescription drugs. The evidence generated from routinely collected data can further enhance our understanding of prescription drug misuse; patient and prescriber behavior, outcomes of misuse and influence policy changes on these issues.

There are no universally accepted definitions of prescription drug misuse [22, 23] making quantification challenging. Due to the limited clinical information held in routine data collections, prescription drug misuse is not directly measured at the population level [23] but is commonly inferred based on patterns of drug access and by investigating patient interactions with prescribers and pharmacies.

In response to concerns about the management of chronic pain treated with opioid analgesics, the US Food and Drug Administration (FDA) has recently sought submissions related to the post-market surveillance of extended release and long acting opioid formulations [24]. In particular, the FDA requested submissions relating to defining misuse, abuse, addiction and their consequences measured in routine data collections [24]. Clearly, synthesizing the global literature will add significant value to this endeavor.

Our timely systematic review aims to examine the measures, extent and factors associated with prescription drug misuse in observational studies based on routinely collected person-level prescription or dispensing data.

2 Methods

2.1 Eligible studies

We included English-language peer-reviewed manuscripts published between January 1 2000 and July 31 2013 satisfying the following criteria:

- Aim or method investigated prescription drug misuse
- Measure of prescription drug misuse derived exclusively from person-level prescription/dispensing data
- Investigated misuse in adult persons (≥18 years)

We excluded grey literature (government reports), case reports, letters, editorials, opinion pieces, reviews and conference abstracts.

2.2 Study identification

2.2.1 Search strategy (Electronic supplementary material resource #1)

We searched MEDLINE, Embase, CINAHL and MEDLINE In Process. We combined keywords and subject headings to identify studies investigating prescription drug misuse measured in routinely collected prescription/dispensing data using observational approaches. Terms included misuse, problematic; prescription drugs; factual databases; population surveillance, cohort studies. We completed three further searches using: Google Scholar [25] (reviewed first 200 results per search), Scopus citations (for articles citing included manuscripts) and screened back references of included studies, review articles and selected excluded studies.

Two reviewers (BB and LM) screened the abstracts and titles of articles to identify potentially relevant studies. These studies were assessed independently (BB and LM) for inclusion in the review

using a 5-item tool based on the eligibility criteria (Electronic supplementary material resource #2). A third reviewer (SP) arbitrated when consensus about inclusion was not reached (18% of articles).

2.3 Data Extraction

Two independent reviewers (BB and LM) completed comprehensive data extraction for articles meeting our eligibility criteria (Electronic supplementary material resource #3). We extracted the following information:

1. Study characteristics: year of publication; publishing journal; observation period (beginning and end year, and duration in months); funding source; objectives; setting; generic names of drug(s) investigated; data source including extent of population coverage, and terminology related to misuse. We also calculated lag time (year of publication minus last year of study).
2. Cohort characteristics: number of cohort(s); cohort size(s); and cohort details including study inclusion/exclusion criteria. Studies reported the extent of prescription drug misuse in drug user cohorts (persons dispensed or prescribed the drug[s] of interest) or in misuse cohorts (persons exhibited behavior considered to be outside the norms of prescription drug use).
3. Measures of prescription drug misuse: the characteristic or behavior of interest (e.g. number of prescribers), threshold defining behavior indicative of misuse as defined by the study authors (e.g. ≥4 prescribers) and time period of assessment (e.g. 6 months).

   We identified each measure as:

   - Stand-alone: investigated a single characteristic or behavior (e.g. the proportion of persons accessing '≥4 prescribers' in 6 months); or
   - Composite: in user cohorts, the measurement of two or more characteristics or behaviors (e.g. the proportion of persons using '≥4 prescribers AND ≥4 dispensing pharmacies' in 6 months). In misuse cohorts (e.g. defined by persons using '≥4 prescribers' in 6 months) the measurement of at least one additional characteristic or behavior (e.g. the proportion of misusers accessing '≥4 dispensing pharmacies' in 6 months).

4. Other prescription drug misuse-related outcomes, e.g. specific drug classes and drugs associated with misuse.
5. Summary statistics: percentages or other statistics (e.g. means with standard deviation or medians with ranges) related to all misuse measures. Where possible we calculated the extent of misuse in user cohorts if not reported in individual studies.
6. Rationale for measure(s) of misuse: any reference to previously published studies; expert panel recommendations; empirical derivation, or any other rationale.
7. Comprehensiveness of reporting (BB only) according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement Checklist for Observational, Population-Based Cohort Studies [26, 27].

2.4 Terminology

In the global literature, a range of terms are used to encapsulate prescription drug misuse including abuse, dependence, diversion, misuse, problematic or non-medical use [1, 28-30]. As such, our search strategies included twenty-four unique misuse-related terms to capture relevant articles. For the purposes of this review we use the umbrella term 'prescription drug misuse' to capture the continuum of misuse, ranging from use above the norms, through to dependence, abuse and diversion. This is consistent with the FDA's terminology in their recent call for submissions on post-market opioid surveillance [24].

2.5 Analysis

In reviewed studies there was considerable variation in study design including: study population(s), medicine(s) of interest, definition(s) of misuse and outcome measures. Due to this variation, it was not possible or appropriate to use traditional meta-analytic approaches to pool individual study results. Instead, we provided a descriptive analysis, detailed the key findings of individual studies and summarized study features in tables and figures. Our review is consistent with AMSTAR and PRISMA reporting criteria (Electronic supplementary material resource #4).

3 Results

3.1 Studies identified

We screened the titles/abstracts of 10,803 articles and reviewed 281 full-text manuscripts. Fifty-two studies met our eligibility criteria; 38 were identified from MEDLINE, Embase, CINAHL or MEDLINE In Process, 2 from Google Scholar, 4 from Scopus citations and 8 from back references (Figure 1). We include the bibliography of the 229 excluded studies (Electronic supplementary material resource #5).

3.2 Study features (Table 1)

The studies were set in the US (27 studies), France (17 studies), Norway (7 studies) or Canada (1 study). All studies from Norway used dispensing data for the entire national population; the other 45 studies used populations within a specific province, state or region. Of the 52 included studies, 32 (61.5%) were published between 2010 and July 2013. The median study observation period was 18 months (range: 4-132 months, IQR: 12-37.5 months) and the median lag time was 4 years (range: 2-15 years, IQR: 3-6 years). Most studies (21) did not report a funding source. The remaining studies were funded primarily by research grants (15), or the pharmaceutical industry (7). Fifty-one studies utilized dispensing data; one study used prescription data. Forty-six unique terms were used by study authors to encapsulate the concept of 'prescription drug misuse' (Box 1).

3.2.1 Prescription drugs of interest (Table 1)

All studies specified the drug class(es) of interest, the majority focused on opioids (35 studies) and/or benzodiazepines (20 studies). Twenty-nine studies further detailed the specific drugs of interest; the most commonly investigated drugs were codeine (10 studies) and/or diazepam (9 studies). Eleven studies investigated a single drug, 5 of which focused on buprenorphine, for the indications of opiate maintenance or pain.

3.2.2 Cohort characteristics

Thirty-nine studies investigated misuse in a drug user cohort (dispensed drug of interest); 17 in a misuse cohort (authors determined drug use of cohort to be above the norms); 14 included both cohort types; and one did not define the user group. Approximately 93 million prescription drug users were observed across the studies with considerable variability in cohort size (less than 100 to >25 million persons). Twenty-six studies used a comparison cohort differing from the other cohort most commonly due to the drug of interest (9 studies); nature, degree or extent of misuse (7 studies) or region of residence (5 studies). Two studies matched the cohorts on specific variables including month of index prescription, geographic area of pharmacy, prescriber specialty, age and/or number of prescriptions (total and for drugs with abuse potential).

3.3 Measures of prescription drug misuse (Table 2; Electronic supplementary material resource #8)

Fifty studies defined a measure with a specific misuse threshold (e.g. ≥4 prescribers). Overall, four behaviors were the basis of the misuse measures, either alone or in combination: number of prescribers; number of dispensing pharmacies; volume of drug(s) dispensed; and/or overlapping prescriptions/early refills.

Twenty-four studies used at least one stand-alone measure of misuse, 46 studies used at least one composite measure of misuse; and 20 studies used both types of measures. Of the 46 studies that used a composite measure, only five reported the proportion of the cohort exhibiting each component of a composite measure [31-35]. The other studies did not detail the relative contribution of each component to the extent of misuse.

3.4 The extent of prescription drug misuse (Electronic supplementary material resource #8)

The extent of misuse ranged from 0.01-93.5%, and was generally higher for stand-alone compared to composite measures (for the latter, individuals needed to exhibit at least two characteristics or behaviors, as opposed to one). The variability in the extent of misuse reported across the studies reflected the heterogeneity in methodology, more specifically: measures and thresholds of misuse, cohort definitions and the time period of assessment.

3.4.1 Measures and thresholds of misuse.

We identified 89 unique definitions of misuse across 50 studies; only 13 measures were utilized in two or more studies (32 studies in total). There appeared to be an attempt to use pre-existing measure(s) of misuse within, but not between, research groups, however, some groups changed their misuse measures between studies.

Sixteen studies reported the number of prescribers and dispensing pharmacies accessed routinely by drug users. As thresholds increased, the proportion of the population exhibiting the behavior decreased (Figures 2a and 2b). Importantly, the highest proportion of drug users visited 1-2 prescribers or pharmacies when accessing their drug(s). Thirteen of these studies defined a threshold of misuse; 9 studies (69.2%) set the threshold of misuse as ≥3 prescribers or dispensing pharmacies. The thresholds defining misuse impact on the extent of the problem reported across studies.

3.4.2 Cohort definition (drug user and misuse cohorts).

Misuse was measured more frequently in drug user cohorts (87 instances) than misuse cohorts (33 instances). The extent of misuse was most commonly <10% for drug users (58 instances; 66.7%) and >20% in misuse cohorts (23 instances; 69.7%). However, the extent of misuse ranged considerably between drug user (0.01-63.2%) and misuse cohorts (0.2-93.5%), reflecting the variation in the measures and thresholds utilized, and the cohort definition. A strict cohort definition increased the reported extent of misuse; misuse cohorts had stricter cohort definitions than drug user cohorts. In general, for drug user cohorts, a high reported extent of misuse reflected a low threshold for misuse and for misuse cohorts, the higher the reported extent of misuse, the stricter the cohort definition.

3.4.3 Time period of assessment.

Measures of misuse were assessed from 7 days to 4 years. The most commonly investigated time period was 12 months, utilized in 44% of instances of reporting misuse. Due to the heterogeneity of

thresholds of misuse and cohort definitions, we were unable to make any further observations concerning the time period of assessment.

3.5 Factors associated with prescription drug misuse (Electronic supplementary material resource #9)

Fifteen studies investigated variations in the extent of misuse based on drug class (four studies), specific drug(s) (12 studies) and/or formulation(s) of interest (three studies).

Four studies compared the extent of misuse across different drug classes based on the same measure of misuse within each study and found opioid misuse was higher than benzodiazepine misuse (no statistical comparisons were performed) [36-39].

Six studies compared the extent of misuse for two or more drugs in the same class. In the opioid class, oxycodone (compared to tapentadol) and methadone (compared to morphine, oxycodone, fentanyl, hydrocodone) had a significantly higher risk of misuse-related behavior [40, 41]. Within the benzodiazepine class, three studies demonstrated that flunitrazepam had the highest extent of misuse compared to several other benzodiazepines [42-44]. Within the antidepressant class, tianeptine had the highest extent of misuse (compared to mianserin) [44]. However, no statistical comparisons were performed in the benzodiazepine or antidepressant studies.

Three studies explored the influence of the drug formulation on the extent of misuse and found a larger proportion of stronger benzodiazepines [42] and short acting opioids [45] were dispensed to a misuse cohort compared to weaker or long acting counterparts, respectively.

3.6 Justification of measures of misuse

Thirty-four studies reported a basic rationale for at least one measure of misuse by either citing previously published work (24 studies) mostly their own; using recommendations of an expert panel

(6 studies); and/or via empirical analysis (14 studies). Ten studies utilized more than one method of justification. Eighteen studies did not report a rationale for their choice of measure of misuse.

3.7 Comprehensiveness of reporting observational studies

The median STROBE score was 27 (range: 19 to 33, IQR: 23-29) out of a possible 36. Many studies did not report basic cohort details including sex (20), age (18) and/or cohort size (8). Studies did not identify how they managed any bias (26), loss to follow up (39), missing data (39) or sensitivity analyses (38). Furthermore, 21 studies did not report the funding source.

Forty studies were published from 2008, after the STROBE statement was published; the median STROBE score was 25.5 (range: 19 to 31, IQR: 22-30) for studies published prior to the STROBE statement and 27 (range: 19 to 33, IQR: 24-29) for studies published post the STROBE publication.

4 Discussion

Our systematic review synthesized the global literature quantifying prescription drug misuse based on population-level, routinely collected data. Our aim was to examine the measures, extent and factors associated with prescription drug misuse. We found a high level of consistency in the behaviors measuring misuse across the 52 studies, reflecting common jurisdictional data holdings and the limited number of variables with the capacity to investigate misuse behavior in routine data collections. However, due to the heterogeneity in thresholds of misuse, cohort definitions and time period of assessment we were unable to make definitive comparisons regarding the extent or factors associated with misuse across time or jurisdictions. Despite this significant limitation in the current literature, going forward, the international research community has the capacity to make significant and timely inroads in this field by developing and harmonizing minimum-reporting standards for a core set of pre-defined metrics. Our review and recommendations are timely and highly pertinent to the recent FDA call for submissions regarding the post-market surveillance of specific prescribed opioids [24].

The harms associated with prescription drug misuse, particularly opioid misuse, have now reached epidemic proportions in many jurisdictions internationally [46, 47]. Despite the escalation in prescription drug use and consequences of misuse across jurisdictions [8, 48, 49], we have limited knowledge about the extent of, and variations in, population-level misuse globally. We propose that a comprehensive and harmonized evidence-base, underpinned by routinely collected data, monitoring the extent of prescription drug misuse, will add significant value to the global effort in quantifying this problem. Moreover, this effort will enhance our understanding of the impact of policy responses attempting to address this problem.

***The use of dispensing claims for post-market drug surveillance is a cost-effective means of monitoring longitudinal, population-level prescription drug use and misuse. Many regulatory and funding agencies globally use dispensing claims to monitor prescription drug use, misuse and/or diversion [23]. In this review we demonstrate routine dispensing data is used increasingly in peer-reviewed literature to explore prescription drug misuse, with over 60% of reviewed studies published since 2010. Findings from population-level routinely collected dispensing/prescription data have the capacity to complement other methodological approaches such as detailed medical record reviews, surveys and in-depth qualitative studies to enhance our understanding of prescription drug misuse. Moreover, linking dispensing claims with other routinely collected health data, such as hospitalizations and vital status will also provide further insight into the risk factors and drug access patterns related to harm.

Our review has several limitations. It is not certain that all relevant studies were captured. We reviewed over 10,000 abstracts and employed a comprehensive search strategy to identify relevant articles [50], 14 were identified through back references, Scopus citations or Google Scholar searches, indicating the challenges of targeted searching and the diversity of keywords and subject headings used across studies and databases. We excluded articles that were not published in English; as nearly half of included studies originated from Europe we may have missed studies published in other languages [51, 52]. Our estimates of prescription drug misuse are solely from the perspective of the

health care payer; we are unable to address access issues outside the dispensing episodes observed in our data set including medication obtained illegally. We applied the STROBE guidelines to all studies, irrespective of publication date. However, the results did not vary considerably for studies published prior to or post STROBE statement publication. We did not undertake a search of journal contents due to the diversity of journals where the studies were published (32 different journals for 52 studies) [52]. These limitations do not impact our key findings. In fact, adding more studies is likely to contribute further to the heterogeneity we found across the field. We categorized studies and metrics to synthesize the disparate literature. For example, we categorized misuse measures as stand-alone or composite measures. All measures based on a single behavior (e.g. ≥4 prescribers in 6 months) applied in a misuse cohort were categorized as composite measures as cohort members were identified as potential misusers. These measures could have been categorized as stand-alone measures. However, this choice impacts on data presentation, not key findings. Finally, a key limitation of the literature is the notable absence of validation to establish whether the proxies actually measure misuse or are associated with harm [23].

Despite these limitations, this is one of the most comprehensive systematic reviews of this field to date. Our review was highly focused on measuring prescription drug misuse in routinely collected data. Other published reviews focused on jurisdiction-specific literature [23, 47, 53-56]; self-report or medical chart data to ascertain use [47, 55-57]; specific drug classes [23, 53, 54, 57] or patient populations [54-57]. The interpretation of these reviews were also impeded by the heterogeneity in study design [54, 56] and/or methods [47, 54-56]. However, the authors of these reviews did not suggest any practical solutions for unifying research in the field. Our recommendations provide a foundation that will increase the dialogue between researchers and unify future routine monitoring and post-market surveillance research (see section 4.1). Our study complements two recent comprehensive reviews; one examining the patient, prescriber and environmental characteristics associated with opioid-related death [54]; and an overview by FDA researchers of the appropriateness of US data sources for measuring prescribed opioid abuse [23].

4.1 Reporting recommendations

We have developed recommendations to harmonize the measurement and reporting of prescription drug misuse in routine data collections. These recommendations were not part of the original study objectives, instead they are underpinned by the learning in this review, particularly the challenges we faced in identifying studies and comparing the extent of misuse across studies (Box 2). Our recommendations center around three key areas: methodology (promotion of consistent metrics to determine appropriate measures of misuse); reporting (listing all drugs by generic name included in each study and the specifics of the misuse measures), and study nomenclature (where possible, consistency in the use of key words including 'prescription drug misuse' that facilitate direct mapping to searchable subject headings). Future studies should combine these recommendations with the current standard reporting requirements for observational studies [26, 27], which will support the current FDA initiative and add value across other jurisdictions.

5. Conclusion

Prescription drug misuse has reached epidemic proportions in the US and is fast increasing in other jurisdictions. Despite the consistency in data holdings and behaviors used to define misuse in routine data collections across jurisdictions, we found considerable variation in measures of prescription drug misuse, cohort definitions and time periods of assessment. The adoption of new or modifications to existing policies targeting prescription drug misuse are much easier to argue for (or against) when the impact is measured robustly and consistent, reproducible effects have been demonstrated across multiple settings. Thus having consistent metrics for prescription drug misuse across jurisdictions is a very simple step, but one with potentially far-reaching consequences.

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Table 1 Characteristics of included studies (N=52 studies)

	N	%
Study setting		
United States	27	51.9
France	17	32.7
Norway	7	13.5
Canada	1	1.9
Year of publication		
2000-2004	7	13.5
2005-2009	13	25.0
2010-2013	32	61.5
Length of observation period for routinely collected data		
< 12 months	5	9.6
12-24 months (inclusive)	28	53.8
25 months to 48 months (inclusive)	11	21.2
49 months to 108 months (inclusive)	7	13.5
>108 months	1	1.9
Lag time (year published - last year of observation)		
1-2 years	4	7.7
3-5 years	34	65.4
6-10 years	8	15.4
> 10 years	6	11.5
Study funding		
Grants: non-government, government or research	15	28.8
Industry: pharmaceutical company	7	13.5
Core government funding	3	5.8
Other	4	7.7

No funding	2	3.8
Not disclosed	21	40.4
Number of prescription drug classes investigated per study		
One	39	75.0
Two	5	9.6
Three	6	11.5
Four	2	3.8
Drug classes investigated for misuse[a]		
Opioids (incl. controlled substances)	35	46.1
Benzodiazepine	20	26.3
Z-drug (zopiclone; zolpidem)	5	6.6
Antidepressant	4	5.3
Other sedative (carisoprodol)	4	5.3
Central nervous system stimulant	3	3.9
Anorectic (diuretic)	2	2.6
Anticholinergic antiparkinson drug	1	1.3
Antipsychotic	1	1.3
Psychotropic (not further specified)	1	1.3

[a] Studies investigated >1 drug type; % represents prevalence of each drug class studied (/76

Table 2 Summary of measures with a defined threshold of prescription drug misuse (N=50 studies)

Measure details (authors defined threshold of misuse behaviour)	Stand-alone measure (24 studies)	Studies	Behaviour used in composite measure (46 studies)	Studies	Total[a]
Number of prescribers (mode: 4; range: 2-7)	9	[34, 41, 58-64]	32	[13, 31, 34, 36-40, 42-45, 59, 61, 62, 64-80]	36
Number of dispensing pharmacies (mode: 4; range: 2-4)	10	[33, 34, 58, 61-64, 81-83]	25	[31, 33, 34, 36-38, 40, 43, 45, 61, 62, 64-67, 69, 72-76, 79, 80, 82, 84]	29
Volume of drug dispensed (including number of dispensings, and dispensed DDD)	14	[32, 35, 59, 61-63, 79, 81, 82, 85-89]	23	[33, 35, 43, 59-62, 64, 66, 67, 69, 71, 73, 74, 76-79, 82, 84-86, 88]	28
Overlapping prescriptions or early refills	6	[31, 32, 36, 62, 89, 90]	21	[32, 36, 39, 40, 42-44, 62, 63, 65, 68-72, 75, 79-81, 89, 90]	22
Use of specific prescribed drug (e.g. alprazolam)	3	[32, 63, 81]	6	[32, 63, 66, 67, 81, 89]	6
Duration of prescription drug use (e.g. >120 days use)	2	[81, 89]	2	[33, 63]	4
Dose escalation (e.g. 50% dosage increase in mean mg of drug in 2 months)	2	[62, 83]	1	[62]	2
Other (Latent analysis based on age, sex and method of payment)	0	–	1	[91]	1

[a] Number of unique studies investigating behavior as a stand-alone and/or composite measure of misuse

Box 1. Terminology used in reviewed studies to describe prescription drug misuse

We noted 46 different terms including: abuser, clinical abuser, decedent, dependence, deviant (behaviour), deviant consumer, doctor shopper/shopping, excess use, excessive dose, excessive use, excessive user, extreme population, forgery behaviour, fraudulent behaviour, heavy shopper, high consumer, high risk use, high usage, high user, inappropriate dispensing, inappropriate prescription, inappropriate use, long term user, misuse, moderate user, multiple prescriber episode, occasional user, overconsumption, overconsumer, overutilization, persistent use(r), pharmacy hopping, pharmacy shopper, potentially aberrant, potentially inappropriate use, potentially problematic use, probably problematic behaviour, problematic use(r), putative acceptable use, questionable activity, recurrent user, repeat user, shopper, shopping behaviour, transgression behaviour, or user.

Box 2. Recommendations for observational studies using routinely collected data to investigate prescription drug misuse

We recommend researchers should state explicitly the following issues in each published manuscript:

Methodology

1. Detail the distribution of the behavior(s) and the rationale for the threshold(s) for misuse

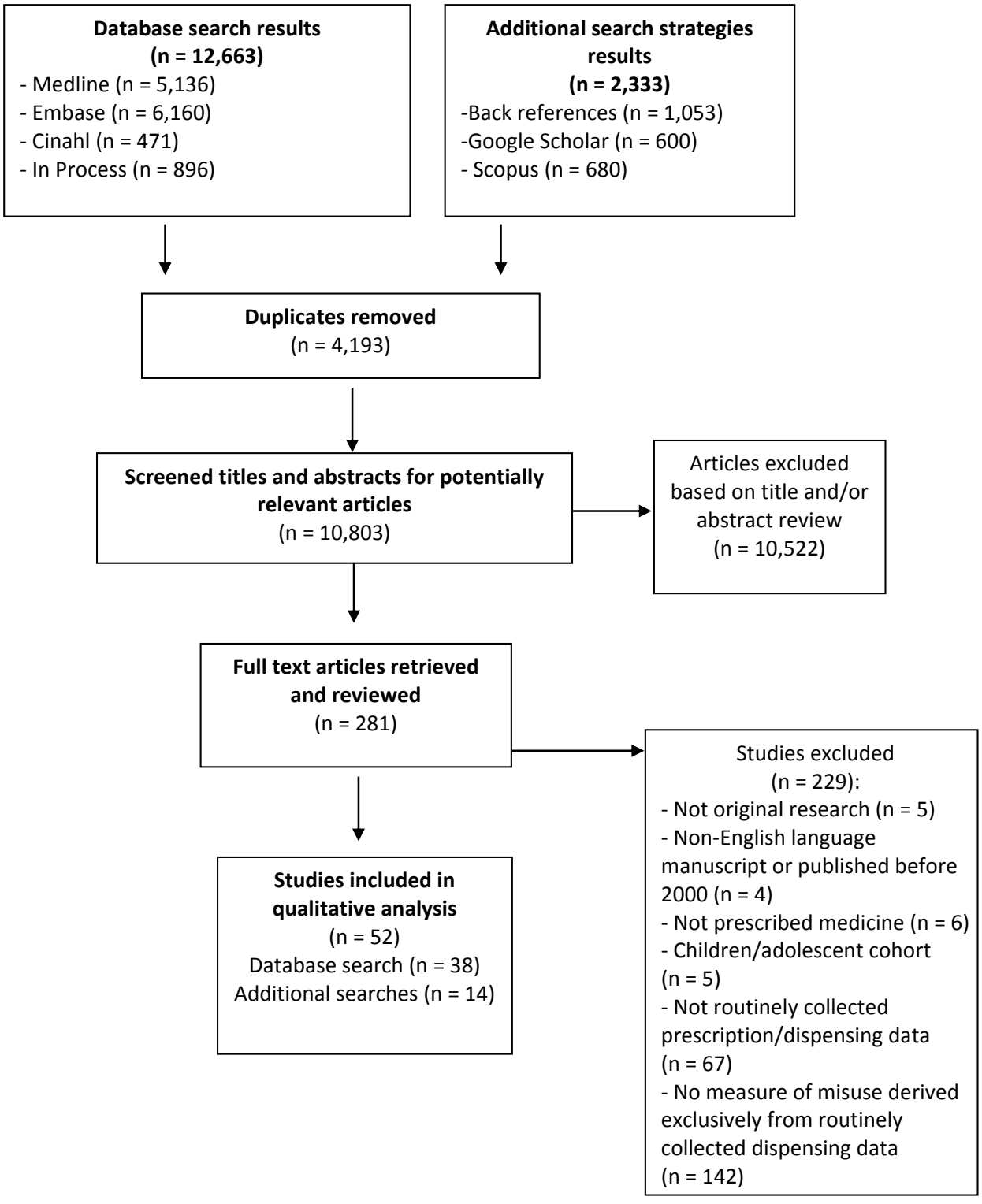
Reporting

2. List the generic name of all prescription drugs studied
3. Detail cohort characteristics for every analysis undertaken
4. Identify all behaviors (variables) and thresholds used to measure misuse
5. State the time period in which the behavior(s) is measured (we recommend that studies should report for a six month period at a minimum)
6. When using a composite measure of misuse, report the extent of misuse for each component and the composite

Study nomenclature

7. Use ‘prescription drug misuse’ as a key word or subject heading

Fig. 1 Flow chart of systematic review methodology to identify included manuscripts



Program utilized to create figure: Microsoft Word.

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Subject:
Author: Bianca Blanch
Keywords:
Comments:
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Fig. 2A Variation in Prevalence of Prescription Drug Access and Misuse According to Number of Prescribers

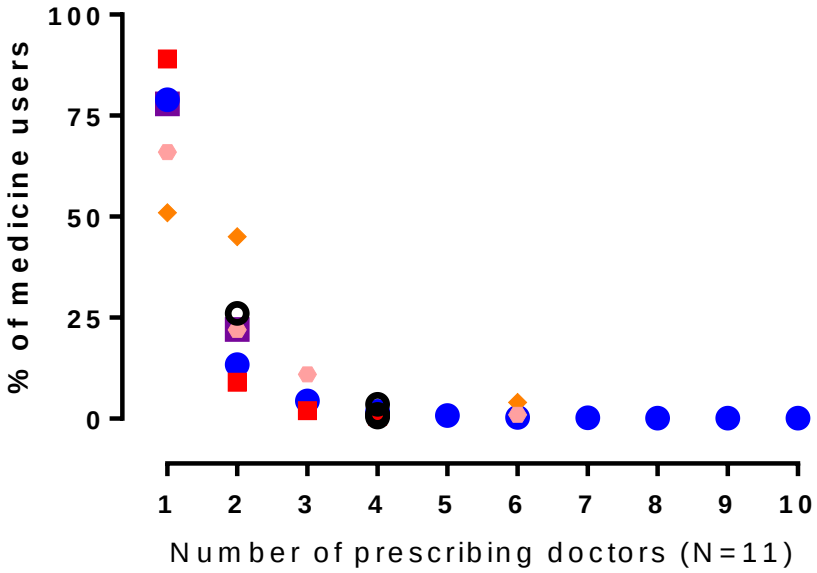
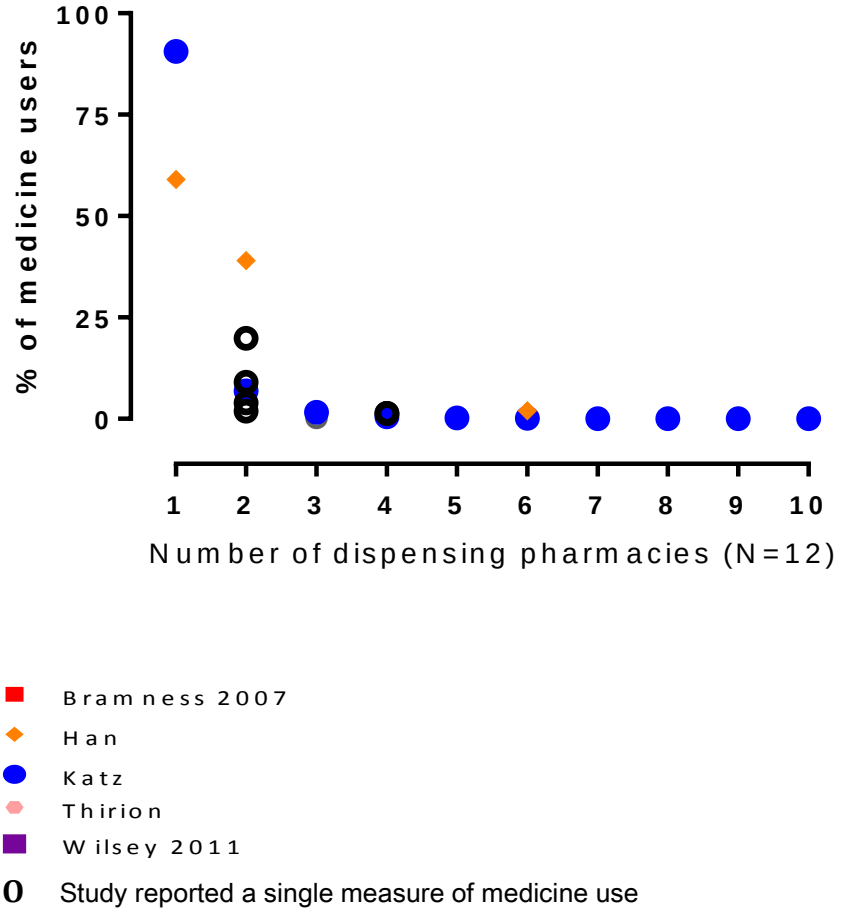


Fig. 2B Variation in Prevalence of Prescription Drug Access and Misuse According to Number of Dispensing Pharmacies



Program utilized to create figure: GraphPad Prism 6.

Title: Harmonizing post-market surveillance of prescription drug misuse: A systematic review of observational studies using routinely collected data (2000–2013).

Journal name: Drug Safety

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Electronic Supplementary Material

Contents Page for Electronic Supplementary Material

Electronic Supplementary Material #1 Detailed Search Strategies Executed in Systematic Review

1. MEDLINE search strategy (N=5,136)[a]			
1. Prescription drug or substance abuse related term	*2. Epidemiology and related methods term*	*3. Routinely collected data*	*4. A prescription drug misuse-related keyword*
Central nervous system agents[b]	Pharmacoepidemiology	Pharmacovigilance	Addic*
Benzodiazepines	Epidemiology	Insurance, health	Abus*
Substance related disorders	Product surveillance, postmarketing	Universal coverage	Misus*
Substance abuse detection	Epidemiological methods	National health programs	Devian*
Polypharmacy	Physician's practice patterns	Health benefit plans, employees	Aberran*
Pharmaceutical services	Drug utilization	Insurance, health, reimbursement	Depend*
Prescription drug misuse	Health services	Centers for Medicare and Medicaid Services	Nonmed*
Prescription drugs	Health services accessibility	Medicaid	Diver*
Drug prescriptions	Public health	Databases, factual	Seek*
	Population surveillance	Insurance coverage	Inapprop*
	Cohort studies	Insurance benefits	Problem*
	Retrospective studies	Single-payer system	Illeg*
	Health services misuse	Reimbursement, incentive	Poison*
		Registries	Selfmed*
		Pharmacies	Inject*
		Drug and narcotic control	Suicid*
		Drug monitoring	Repeat*
		Keywords: Claim* or reimburs*	Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

[a] For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

[b] The subject heading 'central nervous system agents' captures the majority of drug classes associated with misuse. For each search strategy we list any drug class(es) (as subject heading[s]) not captured by 'central nervous system agents'.

2. EMBASE search strategy (N=6,160) [a]			
1. Prescription drug or substance abuse related term	*2. Epidemiology and related methods term*	*3. Routinely collected data*	*4. A prescription drug misuse-related keyword*
Central nervous system agents	Epidemiology	Government	Addic*
Benzodiazepine	Postmarketing surveillance	Insurance	Abus*
Psychotropic agent	Retrospective study	Factual database	Misus*
Central stimulant agent	Drug utilization	Reimbursement	Devian*
Drug dependence	Health care facility	Drug control	Aberran*
Prescription	Health care	Register	Depend*
Polypharmacy	Health service		Nonmed*
Prescription drug	Drug surveillance program		Diver*
Pharmaceutics	Public health		Seek*
Narcotic analgesic agent	Cohort analysis		Inapprop*
			Problem*
			Illeg*
			Poison*
			Selfmed*
			Inject*
			Suicid*
			Repeat*
			Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

[a] For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

3. CINAHL search strategy (N=471) [a]			
1. Prescription drug or substance abuse related term	*2. Epidemiology and related methods term*	*3. Routinely collected data*	*4. A prescription drug misuse-related keyword*
Central nervous system agents	Epidemiology	Insurance, pharmaceutical services	Addic*
Substance use disorders	Epidemiological research	Insurance, health reimbursement	Abus*
Substance abuse detection	Disease surveillance	Insurance, health	Misus*
Polypharmacy	Population surveillance	Insurance benefits	Devian*
Drug dependence	Product surveillance	Insurance coverage	Aberran*
Prescriptions, drug	Drug utilization	Resource databases, health	Depend*
Drugs, prescription	Health resource utilization	Databases, health	Nonmed*
	Practice patterns	Medicaid	Diver*
	Prescribing patterns	United States Centers for Medicare and Medicaid services	Seek*
	Pharmacy service	Medicare	Inapprop*
	Pharmacy and pharmacology	Insurance, Medigap	Problem*
	Public health	Pharmacovigilance	Illeg*
	Retrospective design	Student health services	Poison*
	Health services misuse	Reimbursement, incentive	Selfmed*
	Inappropriate prescribing	Drug monitoring	Inject*
		Key words: Claim* or reimburse*	Suicid*
			Repeat*
			Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

[a] For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

4. MEDLINE In Process search strategy (N=896)[a]			
1. Prescription drug or substance abuse related term	*2. Epidemiology and related methods term*	*3. Routinely collected data*	*4. A prescription drug misuse-related keyword*
Benzodiazepine*	Epidemiol*	Monitor*	Addic*
Prescri*	Pharmacoepi*	Reimburs*	Abus*
Analgesic*	Cohort*	Claim*	Misus*
Opioid*	Retro*	Benefit*	Devian*
Medication*	Population*	Data*	Aberran*
Stimulant*			Depend*
Antidepressant*			Nonmed*
Anipsychotic*			Diver*
Polypharmacy*			Seek*
			Inapprop*
			Problem*
			Illeg*
			Poison*
			Selfmed*
			Inject*
			Suicid*
			Repeat*
			Withdraw*
			Harm*
			Unintent*
			Recreat*
			Shop*
			Hopp*
			Overlap*

[a] For this search strategy: the search terms utilised in each column were combined with 'OR'; the terms between columns were combined with 'AND'.

5. Google Scholar searches (N=600)
“Prescription drug” + excess
“Prescription drug” + misuse
“Prescription drug” + abuse

Electronic Supplementary Material #2 5-item Eligibility Criteria Tool

Initial cover sheet

SYSTEMATIC REVIEW: Prescription drug misuse

REVIEWER INITIALS: _____

1a. First author, year of publication and setting:

1b. Study observation period (s):

1c. Prescription medicines included in study (list all): **If no, prescribed medicine:** ☐ illicit drugs only ☐ OTC only

2. Is the article original research?

☐ yes ☐ no **If no, please circle article type:** Review Letter to the editor Editorial Conference abstract

3. Is the study written in English, and published between 2000 and 2013?

☐ yes ☐ no

4a. Does the study measure prescribed medicine use from a routinely collected data source?

☐ yes ☐ no ☐ unclear

Prescription data source details:

Type of dataset utilised:

☐ dispensing/claims ☐ prescription ☐ other, specify:_____

Dataset name and location:_____

If yes to 4a **— 4b. Is there at least one outcome reporting prescription drug misuse using the data source identified in 4a?**

☐ yes ☐ no ☐ unclear

5. Does the population include adults?

☐ yes ☐ no

⇨ Should the study be included?

If 2-5 are all "yes" ☐ definite

If any of 2-5 are "no" ☐ exclude

If any are "unclear" ☐ probable

If article is excluded:

☐ Consult during write-up of systematic review (i.e. relevant findings or theory)

☐ Read back references (tick if article included a measure of problematic use of medicine but excluded)

Inclusion Criteria:

- Study includes at least one prescribed medicine
- Reports an outcome related to prescription drug misuse
- Routinely collected data is study source for prescribed medicine (s)
- Published between 2000-2013
- English language

Electronic Supplementary Material #3. Data Extraction Tool for Included Studies

SYSTEMATIC REVIEW : Prescription drug misuse

Main Data Extraction Tool

Reviewer initials:_____ **Journal name:**_____

1. Bibliographic and study details

First author surname (year):_____ Study funding source: ☐ Grant (gvt/research) ☐ Industry (Health insurance or pharmaceutical) ☐ No funding ☐ Not recorded/specified ☐ Other, please specify:_____

Study location (continent): ☐ Asia ☐ Africa ☐ North America ☐ South America ☐ Europe ☐ Australia

Further location details specified (i.e. country and/or states included in study):_____

_____

2. Study focus and aims

Reported aim of study (verbatim):_____

_____

_____

_____

_____

Prescribed medicine class(es) of interest (tick all that apply): ☐ Antipsychotic ☐ Antidepressant ☐ Benzodiazepine

☐ Diuretic ☐ Opioid ☐ Central nervous system stimulant ☐ Other medicine class_____

Number of unique medicines investigated in article: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ ≥5 ☐ Class not further specified ☐ Medicines not specified. Specify the generic name of each medicine investigated:_____

_____

_____

_____

3. Study period, data and cohort details

First year of observation:_____ Last year of observation:_____ Longest period of observation: _____months

Data details (not cohort specific)

Number of datasets used to measure outcomes:_____ datasets

Data set or source 1 (name and type, i.e. medicine dispensing data):_____

Number of persons covered by the dataset: _____ people OR Population of region:_____

Percentage of the population covered by the dataset: _____%

Population insured/covered by the dataset (e.g. age, employed, role, location etc)

_____

_____

_____

Data set or source 2 (name and type, i.e. medicine dispensing data):_____

Number of persons covered by the dataset: _____ people OR Population of region:_____

Percentage of the population covered by the dataset: _____%

Population insured/covered by the dataset (e.g. age, employed, role, location etc)

_____

_____

_____

1

Cohort details

Number of cohorts of interest specified (including any comparison groups): _____ cohorts

Prescription drug misuse term used in manuscript (i.e. misuse, abuse, deviant etc):_____

Coverage of data: ☐ National ☐ State/province/region specific ☐ Multiple states/provinces/regions included, number:____

Cohort 1 (name):_____

Cohort definition: ☐ Prescription/dispensing of medicine OR ☐ Pre-defined abuse cohort only

Cohort of interest inclusion criteria:_____

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Cohort of interest exclusion criteria:_____

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Number of persons identified in cohort (%): _____ Mean age (SD):_____ Median age (range):_____

Cohort 2 (name):_____

Cohort definition: ☐ Prescription/dispensing of medicine OR ☐ Pre-defined abuse cohort only

Cohort of interest inclusion criteria:_____

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Cohort of interest exclusion criteria:_____

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Number of persons identified in cohort (%): _____ Mean age (SD):_____ Median age (range):_____

Cohort 3 (name):_____

Cohort definition: ☐ Prescription/dispensing of medicine OR ☐ Pre-defined abuse cohort only

Cohort of interest inclusion criteria:_____

_____

_____

Cohort of interest exclusion criteria:_____

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Number of persons identified in cohort(%): _____ Mean age (SD):_____ Median age (range):_____

4. Misuse outcomes			
Outcome 1	**Indicator includes**		**Reported outcome of indicator**
	Indicator variable(s)	**Specified time period**	
	☐ Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	☐ Number of prescribing doctors		
	☐ Amount dispensed/ prescribed (i.e. DDD)		
	☐ Number of prescriptions		
	☐ Specific medicine or combination: specify _____ _____ _____		
	☐ Overlapping prescriptions		
	☐ Other: specify _____ _____ _____ _____		
Outcome 2	**Indicator includes**		**Reported outcome of indicator**
	Indicator variable(s)	**Specified time period**	
	☐ Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	☐ Number of prescribing doctors		
	☐ Amount dispensed/ prescribed (i.e. DDD)		
	☐ Number of prescriptions		
	☐ Specific medicine or combination: specify _____ _____ _____		
	☐ Overlapping prescriptions		
	☐ Other: specify _____ _____ _____ _____		

Outcome 3	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	☐ Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	☐ Number of prescribing doctors		
	☐ Amount dispensed/ prescribed (i.e. DDD)		
	☐ Number of prescriptions		
	☐ Specific medicine or combination: specify _____ _____ _____		
	☐ Overlapping prescriptions		
	☐ Other: specify _____ _____ _____ _____		

Outcome 4	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	☐ Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	☐ Number of prescribing doctors		
	☐ Amount dispensed/ prescribed (i.e. DDD)		
	☐ Number of prescriptions		
	☐ Specific medicine or combination: specify _____ _____ _____		
	☐ Overlapping prescriptions		
	☐ Other: specify _____ _____ _____ _____		

Outcome 5	Indicator includes		Reported outcome of indicator
	Indicator variable(s)	Specified time period	
	☐ Number of dispensing pharmacies		Definition of prescription drug misuse? Y N
	☐ Number of prescribing doctors		
	☐ Amount dispensed/ prescribed (i.e. DDD)		
	☐ Number of prescriptions		
	☐ Specific medicine or combination: specify _____ _____ _____		
	☐ Overlapping prescriptions		
	☐ Other: specify _____ _____ _____ _____		

Other relevant reported trends/outcomes related to cohort of interest:

Describe other outcome(s) measured	Report finding(s) related to other outcome(s)

5. Other relevant results i.e. prevalence, predictors of use, impact of intervention, characteristics of misusers:

Electronic Supplementary Material #4 A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Electronic Supplementary Material 4a: A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist

Section/topic	#	Checklist item	Reported on page #	Comments
INTRODUCTION				
Was an "a priori" design provided?	1	The research question and inclusion criteria should be established before the conduct of the review.	5-6	
METHODS				
Was there duplicate study selection and data extraction?	2	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	6	
Was a comprehensive literature search performed?	3	At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated, and where feasible, the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	5, ESM 1	
Was the status of publication (i.e., grey literature) used as an inclusion criterion?	4	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	5, 13	
Were the methods used to combine the findings of studies appropriate?	5	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).	X	Not a meta-analysis: Qualitative synthesis
RESULTS				

Were the characteristics of the included studies provided?	6	In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	Tables 1 and 2	
Was the scientific quality of the included studies assessed and documented?	7	''A priori'' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	5, 11-12	
Was the scientific quality of the included studies used appropriately in formulating conclusions?	8	The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	X	Not a meta-analysis: Qualitative synthesis
Was the likelihood of publication bias assessed?	9	An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	X	Not a meta-analysis: Qualitative synthesis
FUNDING				
Was the conflict of interest included?	10	Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	8, 16, Table 1	
APPENDIX				
Was a list of studies (included and excluded) provided?	11	A list of included and excluded studies should be provided.	ESMs 5 and 6	

Electronic Supplementary Material~~Online resource~~ 4 A Measurement Tool to Assess Systematic Reviews (AMSTAR) Checklist and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (continued)

Electronic Supplementary Material~~Online resource~~ 4b: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist

Section/topic	#	Checklist item	Reported on page #	Comments
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1	
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2	No registration number
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5	
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X	No registered protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	ESM 1	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7, ESMs 2 and 3	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7, ESM 3	

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	X	Not a meta-analysis: Qualitative synthesis
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	X	Not a meta-analysis: Qualitative synthesis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	X	Not a meta-analysis: Qualitative synthesis
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Figure 1	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	ESM 7	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	X	Not a meta-analysis: Qualitative synthesis
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	ESM 7	Not a meta-analysis: Qualitative synthesis
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	7-12, Tables 1	

			and 2	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	X	STROBE results 11-12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	X	Not a meta-analysis: Qualitative synthesis
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15	
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16	

Electronic Supplementary Material 5 Reference List of Excluded Studies (N=229)

1. Aeschbach Jachmann C, Jagsch R, Winklbaur B, Matzenauer C, Fischer G. Office-based treatment in opioid dependence: A critical survey of prescription practices for opioid maintenance medications and concomitant benzodiazepines in Vienna, Austria. *European Addiction Research* 2008;**14**(4):206-212.
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of Managed Care 2001;**7**(11):1093-1100.
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Electronic Supplementary Material 6 Reference List of Included Studies (N=52)[a]

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[a]Reference list for Electronic Supplementary Material 7-9

Electronic Supplementary Material 7 Summary of Included Studies (N=52)[a]

First author Year of Publication Setting (Observation period)[b]	Aim(s)[c] (Drug class[es] of interest)	Cohort(s) details[c]	Measures of prescription drug misuse with a defined threshold (time period of assessment)[d]	Other findings relevant to prescription drug misuse (time period of assessment)	
Bachs[1] 2008 Norway (2006)	Describe 'high users' concomitant drug use (opioid).	**A) Cohort** (N=386,836): ≥1 codeine dispensing. Excluded if: cancer patient; incomplete patient identifiers; or, use in hospitals, nursing homes or physician's office.	*1) Moderate/high codeine user (≥120 DDD):* highest 10% of codeine users (12 months) **A)** 10.7% (n=41,459) *2) High drug user:* dispensed ≥100 DDD of BZD and/or ≥15 DDD of carisoprodol (12 months) **A)** 50.1% (n=193,804); 41.9% (n=162,084) dispensed high amount of BZD or carisoprodol; 8.2% (n=31,720) dispensed high amounts of BZD and carisoprodol.	*Moderate/high codeine use and concurrent high use of BZD (≥100 DDD) or carisoprodol (≥15 DDD) by sex: Female: 6.9%-8.1% Male: 4.0%-5.7% *From 10 years of age, females had higher rates of codeine utilization than males.	*In other codeine users (<120 DDD in 12 months): 9.6% received high amounts of BZD (≥100 DDD), carisoprodol (≥15 DDD) or both. *8% of Norwegian population was dispensed a codeine analgesic in 2006.
Bellanger[2] 2013 France (Jul-Dec 2005)	Identify users as over- or normal-drug users and identify characteristics associated with overconsumption (AD and Z-drug).	**A) Tianeptine** (N=7,263): ≥2 tianeptine dispensings. **B) Zolpidem** (N=33,584): ≥2 zolpidem dispensings.	*1) Doctor shopper:* ≥4 prescribers (6 months) **A)** 0.4% (n=32) **B)** 0.9% (n=300) *2) Pharmacy shopper:* ≥4 dispensing pharmacies (6 months) **A)** 1.1% (n=78) **B)** 1.3% (n=438) *3) Excessive user:* excessive use threshold derived from Peaks Over Threshold (POT) model (6 months) Threshold value: proportion (%) of cohort exceeding threshold **A)** 1.1: 7.2% (n=524) **B)** 2.0: 0.9% (n=318)	*Overconsumption risk factors for tianeptine and zolpidem: younger age, pharmacy shopping behavior, consumption of ≥1 anxiolytic drug and R ratio >1 (>1 dispensing per 28 days). *Treatment by a psychiatrist increased the odds of overconsumption for tianeptine by 63%; and for zolpidem decreased the odds of overconsumption by 35.6%.	*Pharmacy shopping increased odds of overconsumption by: 168.5% for tianeptine and 518% for zolpidem users. *The classification rate of POT model: Sensitivity: **A)** 83%; **B)** 90% Specificity: **A)** 81%; **B)** 84% Correctly identified: **A)** 81%; **B)** 85%

Bramness[3] 2007 Norway (2004)	Explore abuse potential of carisoprodol (other sedative).	**A) Cohort** (N=83,713): ≥18 years; ≥1 carisoprodol dispensing. Excluded if use in a hospital, nursing home or physician's office; incomplete doctor/user identifiers.	*1) Carisoprodol abuser (CA):* ≥2 DDD/day in any prescription (not further specified); dispensed <100 DDD of opioids, and dispensed <100 DDD of BZD (12 months) **A)** 1.0% (n=815) *2) BZD abuser/anxiety patient (BA):* dispensed: ≥100 DDD of BZD and <100 DDD of opioids (12 months) **A)** 7.8% (n=6,546) *3) Opioid abuser/pain patient (OA):* dispensed ≥100 DDD of opioids (12 months) **A)** 13.6% (n=11,382) *4) High carisoprodol user:* dispensed >15 DDD of carisoprodol (12 months) **A)** 32.2% (n=26,914) *5) Doctor shopper:* ≥4 prescribers (time period not reported) **A)** 0.5% (n=429) •*In user groups defined above, doctor shopper:* ≥4 prescribers (time period not reported) CA: 4.5% (n=37) BA: 1.1% (n=69) OA: 2.0% (n=228)	**Number of prescribers* (time period not reported) **A)** 1 prescriber: 88.8% (n=74,305) 2 prescribers: 9.1% (n=7,602) 3 prescribers: 1.6% (n=1,377) ≥4 prescribers: 0.5% (n=429) **Prescribed drug by a high volume prescriber:* highest 1% of prescribers in medicine volume (12 months) **A)** 9.4% (n=7,834) CA: 10.8% (n=88) BA: 25.3% (n=1,657) OA: 28.3% (n=3,223) *OAs received 48% of total amount of carisoprodol dispensed in 2004.	*Most carisoprodol was dispensed to users with greater than recommended use who were also dispensed large amounts of BZDs and opioids. *Use of ≥4 prescribers and prescription from a high volume prescriber were more prevalent for drugs with abuse potential, i.e. BZDs and opioids. *High prescribers prescribed 'almost 20%' of drugs with abuse potential, i.e. BZDs and opioids.

Bramness[4] 2010 Norway (2004)	Explore whether total carisoprodol (other sedative) consumption relates to prevalence of excessive carisoprodol use.	**A) Cohort** (N=84,319): ≥18 years; ≥1 carisoprodol dispensings from a pharmacy. Excluded if dispensed from an institution (not further defined).	*1) Excessive carisoprodol user:* dispensed >15 DDD of carisoprodol; used >2 times MRDD (time period not specified); ≥2 carisoprodol dispensings; dispensed <100 DDD of BZD, and dispensed <100 DDD of opioids (12 months) **A)** 1.0% (n=815) *2) Highest 1% of carisoprodol users (dispensed ≥480 DDD of carisoprodol)* (12 months) **A)** 1.1% (n=896) *3) Extreme carisoprodol user:* dispensed >1000 DDD of carisoprodol (12 months) **A)** 0.2% (n=158) *4) Proportion of carisoprodol dispensed to each misuse cohort* (12 months) Excessive user: 4.5% Highest 1%: 18.7% Extreme user: 6.1%	**Correlation between misuse cohort and total carisoprodol consumption* (12 months) Excessive user: 0.74 Highest 1%: 0.81 Extreme user: 0.61 **Correlation between misuse cohort and mean dose* (12 months) Excessive user: 0.67 Highest 1%: 0.70 Extreme user: 0.55 *An increase in amount of carisoprodol sold resulted in an increase in the number of people identified in the extreme user group.	**Proportion overlap between misuse cohorts* (12 months) Excessive user: not reported. Highest 1%: 20% were in extreme group; 7% were excessive users. Extreme user: 4% were excessive users. *45%-64% of variation in prevalence of excessive use was explained by the total sales of carisoprodol.
Cepeda[5] 2012 US (2008 to 18 months after index drug dispensing)	Compare rates of overlapping opioid prescriptions and multiple dispensing pharmacies with BZD (abuse potential) and diuretic ('no abuse potential') users and propose a definition for	**Cohort:** dispensed ≥1 medicine of interest; 3 months of data supplied pre-index prescription; dispensing pharmacy(ies) supplied data over entire observation period. **A) Opioid** (N=25,161,024): dispensed ≥1 opioid. **B) BZD** (N=8,595,179): dispensed ≥1 BZD. **C) Diuretic**	*1) ≥1 days of overlapping prescriptions:* written by ≥2 prescribers (18 months) **A)** 13.1% (n=3,297,891) **B)** 9.8% (n=843,654) **C)** 13.9% (n=1,168,462) •*In persons with ≥1 days of overlapping prescriptions: ≥3 prescribers* (18 months) Opioid: 5.4% (n=176,731) BZD: 2.5% (n=20,928) Diuretic: 3.2% (n=37,164) •*In persons with ≥1 days of overlapping prescriptions: ≥2 dispensing pharmacies* (18 months) Opioid: 21.3% (n=700,840)	**Median days' drug supply* (18 months) **A)** Opioid: 10 **B)** BZD: 30 **C)** Diuretic: 30 *Overlapping prescriptions were more common in persons with history of exposure (H) to medicine, than naïve users (N). Opioid: 38.3% (H); 8.5% (N) BZD: 19.5% (H); 6.0% (N) Diuretics: 17.5% (H); 10.8% (N).	

	shopping behavior that differentiates between drug classes.	(N=8,433,456): dispensed ≥1 diuretic.	BZD: 17.7% (n=149,036) Diuretic: 8.3% (n=97,004) •*In persons with ≥1 days of overlapping prescriptions: ≥3 dispensing pharmacies* (18 months) Opioid: 1.3% (n=44,071) BZD: 1.0% (n=8,167) Diuretic: 0.2% (n=2,431) *2) ≥4 days of overlapping prescriptions* (18 months) **A)** 7.7% (n=1,937,130) **B)** 6.8% (n=587,241) **C)** 11.1% (n=936,922) *3) ≥1 overlapping prescriptions and ≥3 dispensing pharmacies (18 months)* **A)** 0.2% (n=44,071) **B)** 0.1% (n=8,167) **C)** 0.03% (n=2,431)	*Opioid cohort: persons aged 25-64 exhibited shopping behavior (≥2 overlapping prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies) more commonly (0.3%) than older users aged ≥65 years (0.1%); prior opioid users exhibited shopping behavior more commonly (0.8%) than opioid-naïve users (0.1%).	
Cepeda[6] 2012 US (2008 to 18 months after index drug dispensing)	Report prevalence of opioid shopping, heavy opioid shopping behavior, and prescriber characteristics associated with shopping.	**A) Patients** (N=217,851): ≥1 opioid dispensings; 3 months of data pre-index prescription; dispensing pharmacy(ies) supplied data for entire observation period. **B) Prescribers** (N=858,290): prescribers with ≥1 opioid shopper as a patient.	*1) Opioid shopper:* ≥1 days overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (18 months) **A)** The extent of drug users defined as an opioid shopper not reported	**Prescribers* with opioid shoppers as patients* (18 months) **B)** 13.2% (n=113,034); 86.8% of prescribers had no shoppers as patients. **Prescribers with heavy shoppers (≥5 shopping episodes)* as patients (18 months) **B)** 1.7% (n=14,699); 98.3% of prescribers had no heavy shoppers as patients.	**Prescriber characteristics associated with opioid shoppers:* number of patients prescribed an opioid (18-35 users [OR 4.05], 916-1831 [OR 620.13]); male (OR 1.06); aged 70-79 (OR 2.01). *25% of prescribers, prescribed opioids to ≥66 patients, accounting for 82% of shoppers. **Prescriber specialties most associated with opioid shoppers as patients:* pain,

					addiction and emergency medicine.
Cepeda[7] 2013 US (2008 to 18 months after index drug dispensing)	Assess prevalence of shopping behavior in opioid users; how soon shopping behavior occurs after initial opioid exposure; number of events per shopper; preferred opioids; and method of payment.	**A) Cohort** (N=25,161,024): ≥1 opioid dispensings; 3 months of data pre-index prescription; dispensing pharmacy(ies) supplied data over entire observation period.	*1) Opioid shopper:* ≥1 days overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (18 months) **A)** 0.3% (n=75,215) of users accounted for 205,932 shopping episodes. •*In opioid shoppers, proportion of heavy shoppers:* ≥6 shopping episodes (18 months) Opioid shoppers: 9.5% (n=7,157) of users accounted for 44.2% (n=90,997) of shopping episodes	**In opioid shoppers, number of dispensing pharmacies* (18 months) 3 pharmacies: 72.7% (n=54,658) 4 pharmacies: 13.9% (n=10,460) 5 pharmacies: 6.8% (n=5,080) 6 pharmacies: 3.2% (n=2,439) ≥7 pharmacies: 3.4% (n=2,578) **In opioid shoppers, number of prescribers* (18 months) 2 prescribers: 48.1% (n=36,178) 3 prescribers: 31.6% (n=23,790) 4 prescribers: 9.3% (n=6,967) 5 prescribers: 4.5% (n=3,357) ≥6 prescribers: 6.6% (n=4,923)	*Shoppers (44.9%) more frequently paid in cash than non-shoppers (18.5%). *In shoppers, the most utilized opioids: schedule II and III (32.7%); combination formulation (30.7%); and IR and ER (25.2%) *Median of 234 days to first shopping event *Mean 2.7 shopping episodes per shopper *91.7% of subjects with a shopping behavior were aged 19-64 years. *Prior opioid users were 13.7 times more likely to exhibit shopping behavior (1.4% vs. 0.1%) than opioid-naïve users.
Cepeda[8] 2013 US (2009 to 12 months after index drug dispensing)	Compare risk of shopping behavior between tapentadol immediate release (IR) and oxycodone IR	**Cohort:** ≥1 tapentadol or oxycodone dispensing; no opioid dispensed in 3 months pre-index prescription. Excluded: dispensed any other opioid 3 days from index date.	*1) Opioid shopper*: ≥1 days overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (12 months) **A)** 0.2% (n=88) **B)** 0.9% (n=967) *2) Heavy shopper:* ≥5 shopping episodes (12 months)	*Oxycodone users had a higher risk of shopping (3.5 times higher) and heavy shopping behavior (OR 6.9) than tapentadol users. **Mean (SD) shopping episodes per person* (12 months)	**Shopping events exclusively for opioid of interest* (12 months) Tapentadol: 0.6% Oxycodone: 28% *-Mean (SD) days to shopping event* (12 months) Tapentadol: 180.0 (104.6)

	(opioid).	**A) Tapentadol IR** (N=42,940) **B) Oxycodone IR** (N=112,821) Cohorts were matched 1:4 ratio on month of initial exposure, age, geographic area of pharmacy, prescriber specialty.	**A)** 0.01% (n=4) **B)** 0.07% (n=80) •*In opioid shoppers, proportion of heavy shoppers* (12 months) Tapentadol: 4.5% (n=4) Oxycodone: 8.3% (n=80)	**A)** 0.004 (0.1) **B)** 0.02 (0.3) **In opioid shoppers, mean (SD) shopping episodes per shopper* (12 months) Tapentadol: 1.8 (1.9) Oxycodone: 2.1 (2.6)	Oxycodone: 156.1 (100.9)
Cepeda[9] 2013 US (2008 to 18 months after index drug dispensing)	Compare distance travelled to fill opioid prescriptions for shoppers and non-shoppers.	**A) Cohort** (N=10,910,451): ≥3 opioid dispensings; 18 months of data post-index prescription.	*1) Opioid shopper*: ≥1 days overlapping opioid prescriptions, ≥2 prescribers and ≥3 dispensing pharmacies (1 shopping episode) (18 months) **A)** 0.7% (n=75,215); accounted for 8.6% of all dispensed opioids *2) Proportion of heavy shoppers:* ≥5 shopping episodes (18 months) **A)** 0.1% (n=9,435)	**Median miles [km] travelled to fill opioid prescriptions* (18 months) Non-shoppers: 0 [0 km] Shoppers: 83.8 [134.9 km] Heavy shoppers: 199.5 [321.1 km] **Median opioid dispensings* Non-shoppers: 6 Shoppers: 39 Heavy shoppers: 390	**Proportion of users with opioid dispensings from ≥2 states* (18 months) Non-shoppers: 4.2% Shoppers: 19.3% Heavy shoppers: 22.4%
Dormuth[10] 2012 Canada (1993-1997)	Determine if implementing a real-time centralized prescription network (RTCP) reduced rate of potentially inappropriate BZDs and opioid dispensings.	**Cohort:** ≥1 opioid (O) or BZD dispensings for ≥30 tablets **A) O – Social assistance** (N=86,704): users receive social assistance **B) BZD – Social assistance** (N=47,983): users receive social assistance **C) O – aged ≥65 years** (N=199,497)	*1) Proportion of inappropriate dispensings*: ≥2 prescribers and ≥2 dispensing pharmacies for ≥30 tablet dispensings (7 days) **A)** 3.2% (n dispensings not reported) **B)** 1.2% (n dispensings not reported) **C)** 0.2% (n dispensings not reported) **D)** 0.6% (n dispensings not reported)	**Relative change in inappropriate dispensings:* post RTCP implementation (30 months) **A)** -32.8% **B)** -48.6% **C)** -40.1% **D)** -42.4% **Absolute change in inappropriate dispensings per month* **A)** -1.1%	*RTCP implementation associated with large, immediate and sustained reductions in inappropriate opioid and BZD dispensings. *Inappropriate NSAIDs use (comparator medicine) was infrequent and did not change during this time period.

		D) BZD – aged ≥65 years (N=150,699)		**B)** -0.5% **C)** -0.3% **D)** -0.1%	
Feroni[11] 2005 France (Oct 2001-Nov 2002)	Investigate GPs attitudes towards buprenorphine maintenance treatment (BMT) and their BMT patients' propensity to doctor shop (opioid).	**A) Cohort** (N not reported): BMT patients of 345 GPs who participated in a random telephone survey. All GP's BMT patients' data then matched to health insurance data.	No threshold of misuse defined.	*On average, BMT users access 3.1 prescribers in 12 months (range: 1-13). *Doctor shopping was lower for persons starting BMT on ≥8 mg/day, than those who were prescribed <8 mg/day. *Patients whose doctors always or often collaborate with a specialized network/care center had a higher number of prescriptions.	*Doctor shopping correlated with high mean prescriptions per user and shorter average duration of BMT. *Socioeconomic characteristics strongly associated with doctor shopping: more physicians per km^2; fewer people per household; higher unemployment or blue collar workers.
Frauger[12] 2009 France (2001 and 2006)	Estimate clonazepam (BZD) deviant behavior, trends in deviant behavior and characteristics of deviants.	**A) Cohort** (N=26,480): ≥1 clonazepam dispensings.	*1) Deviant group:* defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings and total quantity dispensed (9 months) **A)** *Deviant user:* 1.1% (n=292) *'More deviant' user:* 0.07% (n=19)	**Mean (SD) dispensing pharmacies* (9 months) Deviant: 6.4 (2.8) More deviant: 16.6 (4.3) All other persons: 1.4 (0.7) **Mean (SD) prescribers* (9 months) Deviant: 4.6 (2.2); More deviant: 11.6 (3.7) All other persons: 1.5 (0.8) **Mean (SD) dispensing episodes* (9 months) Deviant: 21.1 (8.3) More deviant: 65.0 (31.4) All other persons: 6.0 (3.0) **Mean (SD) sum of DDD dispensed* (9 months)	**Deviant group characteristics:* younger, male and associated with higher: use of BZDs and buprenorphine; number of prescribers, dispensing pharmacies, deliveries and total DDD dispensed. *The prevalence of deviant behavior increased from 0.9% in 2001 to 1.4% in 2006. *Proportion of clonazepam dispensed to deviant group increased from 7.8% (2001) to 9.5% (2009).

				Deviant: 392.1 (200.3) More deviant: 1379.7(1014.1) All other persons: 54.6 (51.3)	
Frauger[13] 2011 France (2005-2008)	Describe patterns of methyl-phenidate (CNS stimulant) use and rates of abuse and diversion.	**A) Cohort** (N=3,574): ≥1 methylphenidate dispensings.	*1) Deviant group:* defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings and total quantity dispensed (9 months) **A)** 1.1% (n=40)	**Mean (SD) dispensing pharmacies* (9 months) Deviant: 11.0 (4.9) All other persons: 1.3 (0.6) **Mean (SD) prescribers* (9 months) Deviant: 12.0 (4.4); All other persons: 1.8 (0.9) **Mean (SD) dispensing episodes* (9 months) Deviant: 41.9 (14.7) All other persons: 6.4 (4.5)	**Mean (SD) sum of DDD dispensed* (9 months) Deviant: 1707.6 (585.3) All other persons: 170.5 (150.6) *Proportion of deviant behavior increased over study period, peak of 2.0% in 2007. *Deviant group characteristics: higher utilization rates of BZD, AD, antipsychotic or opioid maintenance therapy.
Fredheim[14] 2009 Norway (2004-2006)	Identify 'problematic' codeine (opioid) prescription patterns.	**A) Naïve users** (N=222,929): ≥1 codeine dispensings in 2005. Excluded: prescriptions with incomplete identifiers or prescribed for cancer. **B) Old users** (N=162,261): *A)* and ≥1 codeine dispensings in 2004.	*1) High user: dispensed >365 DDD of codeine* (12 months) **A)** 0.03% (n=64) **B)** 5.8% (n=9,384) •*In high users: dispensed >100 DDD of BZDs* (12 months) Naïve users: 29.7% (n=19) Old users: 50.5% (n=4,738) •*In high users: dispensed >15 DDD of carisoprodol* (12 months) Naïve users: 18.8% (n=12) Old users: 30.2% (n=2,838) •*In high users: dispensed >730 DDD of codeine* (12 months) Naïve users: 1.6% (n=1) Old users: 19.0% (n=1,786)	*Persons with >730 DDD per year of codeine frequently co-medicated with other drugs including BZDs (66%) and carisoprodol (45%). *0.5% of persons prescribed codeine developed serious problematic use.	

Gilson[15] 2012 US (2000-2006)	Investigate if changes to prescription monitoring program influences: i) prescribing rate for nine schedule II long-(LA) or short acting (SA) opioids, or ii) incidence of multiple provider episodes (MPEs).	**A) Cohort** (N not reported): inclusion/exclusion criteria not specified. Prescription level data (N=15,506,651)	*1) <u>Prescriptions</u> involved in multiple provider episodes (MPEs):* ≥2 prescribers for same opioid and ≥2 dispensing pharmacies (30 days) 9.6% (n prescriptions=1,488,639)	**Prescriptions* dispensed involving MPEs* (time period not reported) SA hydromorphone: 15.2% SA fentanyl: 11.4% SA oxycodone: 10.9% SA morphine: 10.0% LA oxycodone: 8.7% Methadone: 8.6% LA morphine: 8.5% LA fentanyl: 8.1% Meperidine: 7.0%	*Policy change increased rate of MPEs involving all opioids. *Replacing triplicate forms with a secure tamper resistant form increased prescribing rates for SA hydromorphone, meperidine, SA oxycodone. Prescribing rates unchanged for SA or LA fentanyl, methadone, SA or LA morphine and LA oxycodone.
Gjerden[16] 2009 Norway (2004)	Investigate use and potential abuse of antiparkinson (AP) drugs.	**Cohort** (N=73,964): aged 18-69 **A)** (N=70,937) Dispensed any antipsychotic drug **B)** (N=2,771) Dispensed dopaminergic or anticholinergic AP drug reimbursed for Parkinson's disease **C)** (N=213) Dispensed antipsychotic and evidence of Parkinson's disease **D)** (N=43) Dispensed anticholinergic	*1) Proportion of medicine volume consumed by highest 1% of users:* a figure >15% is a strong signal for medicine abuse (12 months) Biperiden: 6.2% BZDs: 16.5% Orphenadrine: 5.4% *2) Doctor shopper:* ≥3 prescribers for BZD tranquilizers (12 months) No meaningful data derived.	**Maximum number of BZD-prescribers* (12 months) **A)** 8 **B)** 5 **C)** 3 **D)** 6 *Antipsychotic drug users accounted for 94% of anticholinergic use, compared to 4.3% of antipsychotic drug user's with Parkinson's disease. *BZD use more frequent in antipsychotic drug users than antipsychotic drug users with Parkinson's disease.	

		medicine, not dispensed an antipsychotic, no evidence of Parkinson's disease. Excluded if: dispensed benzhexol, procyclidine or trihexyphenidyl.		*Cohort D had highest rate of BZD concomitant use.	
Goodman[17] 2005 US (Jun 2000-Jul 2002)	Determine if a prescription review could identify cases of possible oxycodone ER abuse (opioid).	**A) Cohort** (N not reported): ≥1 oxycodone ER dispensing from a Veteran's Affairs (VA) facility. Case level data (N cases = 60,955)	Proportion of cases meeting criteria. *1) Dispensed large quantity*: ≥480 tablets per prescription (20 months) **A)** 5% (n=4 cases) *2) Multiple sites:* prescription for same medicine filled ≥10 days early from ≥2 facilities (25 months) **A)** 24% (n=41 cases) *3) Multiple Veterans Integrated Service Networks (VISNs):* prescription for same medicine filled ≥10 days early from ≥2 VISNs (10 months) **A)** 15% (n=6 cases) *4) High usage:* ≥480 tablets per prescriptions, high dosage (320 mg daily), or frequent dosing intervals (every 4-6 hours): extent of misuse not reported *5) Early refills:* ≥2 consecutive early refills from ≥2 providers: extent of misuse not reported *6) Large total quantity:* ≥480 tablets total per month: extent of misuse not reported	**Cases involving past/present substance abuse diagnosis per measure of misuse* (time period not reported) Dispensed large quantity: 3% (n=2 cases) Multiple sites: 5% (n=8 cases) Multiple VISNs: 5% (n=2 cases) <u>Doctor's</u> aberrant prescribing pattern as indicator. **Doctors prescribed large quantity:* ≥480 tablets per prescription (20 months) 12% (n=10 cases) **Multiple sites:* <u>doctor</u> aberrant prescribing not defined (25 months) 2% (n=3 cases)	**Multiple VISNs:* <u>doctor</u> aberrant prescribing not defined (10 months) 2% *The prevalence of aberrant drug-related behavior of multiple sites or multiple VISNs decreased over the review periods.
Hall[18] 2008 US (2006)	Evaluate characteristics of persons dying from	**A) Cohort** (N=295): died of unintentional drug poisoning according to death certificate in	*1) Doctor shopper*: ≥5 prescribers of controlled substances (12 months) **A)** 21.4% (n=63)	**Diverters*: pharmaceuticals used without a prescription record (12 months) **A)** 63.1% (n=186)	*Unintentional overdose death rate: 16.2/100,000 *Doctor shopping associated with: being

	unintentional pharmaceutical overdose (controlled substances), types of drugs involved and the role of drug abuse in deaths.	2006. Excluded: no autopsy performed; toxicology tests not performed by Office of Medical Examiner; overdose due exclusively to illicit drugs, over the counter products and/or alcohol.		*Diverter and doctor shopper* (12 months) **A)** 8.1% (n=24) *Deaths involving specific medicine classes* (12 months) Opioid analgesic: 93.2% Psychotherapeutic: 48.8% Other prescription drug (butalbital, carisoprodol, cyclobenzaprine, diltiazem, phenytoin, promethazine): 11.2%	female (OR 2.2); aged 35-44 years (OR 2.0); previous overdose (OR 2.8). *Diversion behavior associated with: 18-24 age group (OR 12.1) never marrying (OR 2.8); history of substance abuse (OR 1.8); non-medical route of pharmaceutical administration (OR 1.9) or illicit drug use (OR 2.1).
Han[19] 2012 US (2005-2007)	Examine effect of individual and county related factors on use of multiple prescribers and/or pharmacies for prescription opioids.	**A) Cohort** (N=1,057,012): ≥1 opioid dispensings per year (2005 to 2007). Excluded if: incomplete/ implausible prescription; commercial transaction; non-standard route of administration for chronic pain users; drug use by age group not associated with chronic pain or obtaining drugs through office interactions.	No threshold of misuse defined.	*Number of prescribers* (12 months) **A)** Mean (range): 2.1 (1-158) 1 prescriber: 50.7% (n=536,408) 2-5 prescribers: 45.1% (n=476,843) ≥6 prescribers: 4.1% (n=43,761) *Number of dispensing pharmacies* (12 months) **B)** Mean (range): 1.8 (1-100) 1 pharmacy: 59.0% (n=623,357) 2-5 pharmacies: 38.9% (n=411,704) ≥6 pharmacies: 2.1% (n=21,951) *Higher number of prescribers and dispensing pharmacies associated with:	*Physician availability was the most robust predictor, i.e. as number of physicians increased so did number of prescribers and dispensing pharmacies. *Individuals who use both schedule II and III opioids visited multiple prescribers and multiple pharmacies more often than those who used opioids from a single schedule. *Higher use of multiple prescribers and pharmacies associated with: ethnicity, educational attainment, median household income and physician availability.

				younger age (18-74), being female, living in a county with more licensed physicians and surgeons.	
Hartz[20] 2009 Norway (2004-2007)	Examine association between disability pensioners using BZD and aspects of problematic use.	**A) Cohort** (N=19,520): aged ≤61 years; ≥1 BZD dispensing; health survey data linked to national prescription database. Excluded if: reimbursed for cancer drugs; died/emigrated prior to 2004; BZD user at survey baseline; wrote trade names for BZD in survey; missing disability status.	*1) Long term user:* dispensed ≥1 BZD each year between 2004 and 2007 (48 months) **A)** 2.2% (n=425)	*In long term users, median BZD use was higher in disability pensioners (50 DDD) than non-disability pensioners (20 DDD). *When controlling for other factors, long term use of BZD is more prevalent in disability pensioners than non-disability pensioners (OR 2.5).	*Predictors of long-term BZD use: being female and increasing age. *Use of BZD and other potentially addictive drugs (z-drugs, opioids and carisoprodol) increased over the 4 years.
Hoffman[21] 2003 US (1998-Mar 2000)	Evaluate effectiveness of physician alert to reduce patients' excessive use of prescription drugs and decrease costs to the third party payer (controlled substances schedule II to IV).	**A) Control** (n=89): ≥1 alert. **B) Excessive users** (n=94): letter sent to physician; user has ≥3 alerts in 3 months (alerts relate to number of prescribers, pharmacies and volume of drug dispensed); no concurrent medication use indicative of cancer, HIV infection or renal failure. Excluded if: Medicare user; <6 of collected data.	*1) Recurrent excessive users:* ≥2 letters sent out to physician (6 months) **B)** 29.8% (n=28)	**Number of prescribers* (3 months) Pre-intervention mean (SD) to post-intervention mean (SD) [% change] **A)** 5.3 (2.4) to 1.4 (2.4) [-22.0%] **B)** 6.4 (3.6) to 2.2 (3.3) [-28.0%] **Number of prescriptions* (1 month) **A)** 13.4 (3.5) to 3.7 (4.7) [-28.4%] **B)** 13.7 (6.4) to 5.0 (4.4) [38.1%] **Number of high abuse*	**Prescription drug cost* (1 month) **A)** $460.15 ($335.00) to $39.07 ($331.00) [-17.9%] **B)** $480.28 ($393.00) to $118.38 ($296.00) [-23.1%] **Medical cost* (12 months) **A)** $8811.90 to $970 [not reported] **B)** $9115.96 to $1413.00 [not reported] *23% of users whose physicians received letters did not show any change in dispensing patterns. *Authors attributed control

		Cohorts matched on total number of prescriptions and number of prescriptions with abuse potential.		*prescriptions* (1 month) **A)** 5.5 (2.1) to 2.0 (2.6) [-33.6%] **B)** 6.0 (2.8) to 3.1 (4.6) [-45.5%]	group results to 'regression toward the mean'.
Katz[22] 2010 US (Jul 1995- Jun 2006)	Evaluate trends in schedule II opioid prescribing and dispensing.	**A) Cohort** (N=562,592): ≥1 opioid dispensings in 2006. Excluded if: entry missing prescriber number, date filled, prescription number, quantity, national drug code, days of supply, valid date of birth or customer ID.	*1) Questionable activity:* ≥3 prescribers and ≥3 dispensing pharmacies (12 months) % persons; % prescriptions; % dosage units **A)** 1.6% (n=8,797); 7.7% (n=112,381); 8.5% (n=7,622,840) *2) Preferred indicator: Questionable activity:* ≥4 prescribers and ≥4 dispensing pharmacies (12 months) **A)** 0.5% (n=2,748); 3.1% (n=45,102); 3.1% (n=2,805,613) *3) Questionable activity:* ≥5 prescribers and ≥5 dispensing pharmacies (12 months) **A)** 0.2% (n=1,149); 1.5% (n=22,075); 1.4% (n=1,247,666) *4) ≥1 early refills:* two consecutive prescriptions for same drug with number of days between prescriptions being >10% lower than number of days of supply in first prescription, i.e. if prescription for 30 days, second prescription filled <27 days after first dispensing) (time period varied based on length of prescription) Mean (SD): 0.1 (0.67) **A)** 6.9% (n=38,819)	**Number of prescribers* (12 months) **A)** Mean (SD): 1.4 (0.93) 1 prescriber: 78.9% (n=443,956) 2 prescribers: 13.4% (n=75,191) 3 prescribers: 4.4% (n=24,919) 4 prescribers: 1.8% (n=9,980) 5 prescribers: 0.8% (n=4,274) 6 prescribers: 0.3% (n=1,887) 7 prescribers: 0.2% (n=1,025) 8 prescribers: 0.1% (n=543) 9 prescribers: 0.1% (n=296) ≥10 prescribers: 0.1% (n=520) *76.9% of users with one prescriber accessed one pharmacy; 0.1% of users with one prescriber accessed ≥4 dispensing pharmacies. *Among persons using ≥5 prescribers, 14.1% used ≥4 dispensing pharmacies. *Among persons using ≥10 prescribers, 69.2% used ≥4 dispensing pharmacies.	**Number of dispensing pharmacies* (12 months) **A)** Mean (SD): 1.1 (0.52) 1 pharmacy: 90.6% (n=509,818) 2 pharmacies: 6.9% (n=38,865) 3 pharmacies: 1.6% (n=8,870) 4 pharmacies: 0.5% (n=2,917) 5 pharmacies: 0.2% (n=1,138) 6 pharmacies: 0.1% (n=464) 7 pharmacies: 0.04% (n=248) 8 pharmacies: 0.02% (n=108) 9 pharmacies: 0.01% (n=76) ≥10 pharmacies: 0.02% (n=87) *Rate of questionable activity increased between 1996-2002 and decreased between 2002-2006, despite an increase in opioid prescribing. *SA oxycodone was the

				*11% of total population received ≥1 schedule II opioid in 2006.	opioid most associated with questionable activity.
Logan[23] 2013 US (2009)	Determine prevalence of opioid misuse and the inappropriate prescription practices by emergency department (ED) providers.	**A) Cohort** (N=400,288): aged 18-64; ≥1 opioids dispensed same day as ED visit that was not part of a hospital admission. Excluded if: incomplete information; claims for services which could not render opioids; tests not confirming diagnostic information; not continuously enrolled in health plan for 2009; or treatment for cancer pain determined by ICD-9 diagnosis for cancer.	*1) ≥2 overlapping ED opioid prescriptions:* overlapping by ≥7 days (12 months) **A)** 2.1% (n=8,229) *2) Overlapping ED opioid and BZD prescriptions:* overlapping by ≥7 days (12 months) **A)** 1.0% (n=3,867) *3) ≥1 incidents of LA/ER opioid dispensed for acute pain condition* (12 months) **A)** 0.1% (n=565) *4) Dispensed high opioid doses from ED:* daily dose of ≥100 morphine milligram equivalent (12 months) **A)** 7.8% (n=31,117)	**<u>Prescriptions</u> overlapped with another LA opioid prescriptions:* overlapping by ≥7 days (12 months) **A)** 14.6% **≥2 opioid-related ED presentations* (12 months) **A)** 8% (n=32,024) **Number of ED opioid prescriptions* (12 months) **A)** 1 prescription: 91.0% 2 prescriptions: 7.0% ≥3 prescriptions: 2.0%	*A higher proportion of females (11.5%) had at least one indicator of potentially inappropriate prescribing or misuse, compared to males (9.0%).
Mailloux[24] 2010 US (Jul 1998–Aug 1999)	Identify persons abusing controlled substances (opioids, BZDs, and CNS stimulants) through a decision support tool. Abuse determination based on number of	**A) Intermediate abusers** (N=85): letter sent to physician to alert them to their patients' behavior **B) Abusers** (N=39): no change from 'intermediate abuser' behavior within 6 months, individual is 'locked-in,' i.e. for 2 years one prescriber and one dispensing	*1) Shopping behavior:* medicine obtained by 'multiple providers and pharmacies' (6 and 2 months) *i)* Mean (SD) days of overlapping prescriptions (6 months) **A)** 155.8 (103.1) **B)** 768.2 (609.2) *ii)* Mean (SD) days of overlapping prescriptions (2 months) **A)** 70.8 (55.4) **B)** 350.8 (246.1) *2) Early refill:* same medication obtained from one physician and multiple	**Mean (SD) duplicate prescription score*: number of duplicate prescriptions (controlled substance obtained from different prescribers/pharmacies on the same day) (time period not reported) **A)** 0.3 (0.6) **B)** 1.2 (1.5) **Mean (SD) dispensing pharmacies* (time period not reported)	**Mean controlled substances claims* (time period not reported) **A)** 22.3 (10.4) **B)** 48.7 (18.6) *Overall the classification rate is 95.3%. (Sensitivity: 87.2%, specificity: 96.5%.) *Number of dispensing pharmacies was the best predictor of abuse of controlled substances.

	prescribers, pharmacies, volume of drug dispensed and medical diagnosis.	pharmacy. Excluded if: 'lock-in' required informed consent, part of mental health commitment or condition of probation/parole.	pharmacies within 50% of the days' supply of the first prescription (6 and 2 months) *i)* Mean (SD) episodes (6 months) **A)** 1.9 (2.5) **B)** 5.9 (13.4) *ii)* Mean (SD) episodes (2 months) **A)** 0.6 (1.0) **B)** 3.1 (6.6)	**A)** 4.2 (1.8) **B)** 9.9 (4.3) **Mean (SD) prescribers* (time period not reported) **A)** 4.8 (2.7) **B)** 12.2 (6.5)	
Martin[25] 2011 US (2000-2005)	Report rates of opioid misuse, discontinuation (≥182 days of no opioid use), and identify factors associated with discontinuation.	**A) Commercially insured** (N=23,41): ≥1 chronic opioid use episode, i.e. >90 days of opioids supplied in any 6 month period between Mar 2001-Dec 2004, continuous enrolment for 12 months pre-and post-index date (first opioid dispensing), identified in HealthCore dataset. **B) Publically insured** (N=6,848): *A)* but identified in Arkansas Medicaid.	*1) Opioid misuse score:* based on excess days supplied short- and long-acting opioids, number of dispensing pharmacies, and number of prescribers (6 months) Score 0-1: no misuse **A)** 83.2% (n=19,474) **B)** 87.7% (n=6,003) Score 2-3: possible misuse **A)** 14.5% (n=3,399) **B)** 10.9% (n=747) Score ≥4: probable misuse **A)** 2.2% (n=523) **B)** 1.4% (n=98)	**Prevalence of opioid abuse disorder* (time period not reported) **A)** 0.6% (n=130) **B)** 0.5% (n=36) *Approximately 1/7 persons potentially misuse opioids. *Commercially insured cohort: persons with possible or probable opioid misuse were 20% less likely to discontinue opioids than those with no indication of opioid misuse.	
McDonald[26] 2013 US (2008)	Estimate prevalence of users obtaining opioid prescriptions from different physicians.	**A) Cohort** (N='13.6 million'): ≥1 opioid dispenings in first 60 days of 2008.	*1) Extreme outlying population:* determined by latent class analysis based on method of payment, gender, age (10 months) **A)** 0.7% (n≈95,200), accounting for 1.9% of dispensed medicine.	**Number of prescribers for 57% of users dispensed an opioid after first 60 days of 2008* (10 months) 1 prescriber: 31% 2 prescribers: 14% 3-4 prescribers: 8.6%	*Users 'aged mid to late 20s were 10 times more likely to fit the extreme profile than users double their age'. *In the extreme population, the average

				(inferred) 5-9 prescribers: 3% 10-19 prescribers: 0.4% ≥20 prescribers: 0.04% **Mean number of prescribers for extreme population* (10 months): 10.4	number of prescribers increased with age until age 40, after which it declined.
Nordmann[27] 2013 France (2008)	Describe and compare opioid abuse using doctor shopping to estimate abuse in three French regions.	**A) PACA** (N=885,941): ≥1 opioid dispensings; resident of Provence-Alpes-cote d'Azur (PACA) **B) RA** (N=945,102): *A)* except resident of Rhone Alps (RA). **C) MP** (N=386,834): *A)* except resident of Midi-Pyrenees (MP). **D) Entire cohort** (N= 2,217,877): *A) + B) + C)*	*1) Doctor shopping quantity (DSQ)*: amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months) **A)** 213.3 DDD/1000 population **B)** 115.1 DDD/1000 population **C)** 106.2 DDD/1000 population **D)** 150.5 DDD/1000 population Drug class: DSQ (DDD/1000 population) (% of all dispensed drug) Weak opioid analgesics: 75.5 (50.2%) OMT opioids: 55.3 (36.7%) Strong opioid analgesics: 19.7 (13.1%) *2) Doctor shopping indicator (DSI):* proportion of total drug dispensed obtained by overlapping prescriptions from ≥2 prescribers (12 months). DSI <1% is not a signal for abuse. Drug class: DSI OMT: 6.2% Strong opioid analgesics: 5.0% Weak opioid analgesics: 1.1%	**DSQ by opioid* (12 months) Drug: DSQ (DDD/1000 population) **D)** Buprenorphine (OMT): 50.3 Dextropropoxyphene: 27.6 Codeine: 24.1 Tramadol: 23.3 Morphine: 17.8 Methadone: 4.9 Oxycodone: 1.5 Dihydrocodeine: 0.5 Buprenorphine (analgesic): 0.2 Hydromorphone: 0.2	**Specific opioids with DSI≥1%* (12 months) **D)** Buprenorphine (OMT): 8.0% Morphine: 5.5% Dihydrocodeine: 3.7% Buprenorphine (analgesic): 2.9% Oxycodone: 2.7% Codeine: 2% Methadone: 1.9% Hydromorphone: 1.8% Tramadol: 1.1% **DSQ was 2-fold higher in PACA than RA and MP. **Tramadol and dextropropoxyphene DSI show a very low signal of abuse.
Parente[28] 2004 US (2000)	Develop indicators of controlled substance	**A) Cohort 1** (N=2,927,237). **B) Cohort 2** (N=782,800).	*1) ≥6 prescribers of same drug* (time period not reported) **A)** 0.2% (n=6,148) **B)** 0.3% (n=1,957)	**These measures are not a direct measure of misuse, but direct attention to potential problems to	

	misuse for general population (excluding persons with ≥3 prescriptions for injectable opioid without a cancer diagnosis in 12 months and persons dispensed a BZD or opioid with a substance abuse diagnosis)	Inclusion/exclusion criteria not specified.	*2) ≥4 dispensing pharmacies for same drug* (time period not reported) **A)** 0.1% (n=3,806) **B)** 0.1% (n=1,096) *3) ≥4 prescriptions of carisoprodol* (6 months) **A)** 0.1% (n=3,805) **B)** 0.1% (n=862) *4) Continuous overlap of ≥2 different BZDs for ≥90 days* (time period not reported) *i)* when 1 BZD is alprazolam **A)** 0.1% (n=1,757) **B)** 0.1% (n=548) *ii)* when 1 BZD is clonazepam **A)** 0.01% (n=147) **B)** 0.01% (n=58) *iii)* when 1 BZD is diazepam **A)** 0.003% (n=88) **B)** 0.004% (n=32) *5) ≥4 grams/day of acetaminophen* (time period not reported) **A)** 0.03% (n=878) **B)** 0.01% (n=79) *6) ≥2 prescriptions for meperidine hydrochloride with >2 days' supply* (time period not reported) **A)** 0.02% (n=585) **B)** 0.02% (n=157) *7) ≥4 prescriptions of butorphanol* (6 months) **A)** 0.02% (n=585) **B)** 0.02% (n=157) *8) Overlap of ≥2 different sustained*	determine if intervention is needed.	

			release or LA opioids for ≥90 consecutive days (time period not reported) **A)** 0.001% (n=30) **B)** 0.001% (n=8)		
Pauly[29] 2011 France (2006)	Compare two methods to measure deviant behavior when obtaining high dosage buprenorphine (HDB) (opioid).	**A) Cohort** (N=6,519): ≥1 dispensing of HDB.	*1) Deviant persons:* defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings and total quantity dispensed (9 months). **A)** 6.0% (n=390) *'More deviant' persons:* 0.3% (n=21) *2) Proportion of dispensed HDB obtained by DSI:* *Deviant:* 40% (i.e. 60% not obtained by DSI) *More deviant:* 72% (i.e. 18% not obtained by DSI) *Entire cohort:* 13.2%	**Mean (SD) prescribers* (9 months) Deviant: 6.5 (2.2) More deviant: 16.4 (5.7) **Mean (SD) dispensing pharmacies* (9 months) Deviant: 8.2 (3.3) More deviant: 27.5 (9.5) **Mean (SD) dispensings* (9 months) Deviant: 36.9 (16.7) More deviant: 90.0 (32.0)	* *Mean (SD) total quantity dispensed (mg)* (9 months) Deviant: 6,815 (4,462) More deviant: 33,720 (14,432) *Deviant group are: younger, male, dispensed a higher proportion of flunitrazepam, bromazepam, clonazepam and ADs.
Pauly[30] 2011 France (2008)	Analyze and compare diversion and abuse of 14 BZDs through a multi-indicator approach.	**A) Cohort** (N not reported): ≥1 BZD dispensings.	*1) Deviant persons:* defined by cluster analysis profiling individuals by number of: dispensing pharmacies; prescribers; dispensings and total quantity dispensed (9 months). *BZD with highest % of deviant users:* Flunitrazepam: 9.1% *2) Doctor shopping indicator (DSI):* proportion of total drug dispensed obtained by DSQ: amount of excess drug obtained by overlapping prescriptions and ≥2 prescribers (12 months). *BZD with highest DSI:* Flunitrazepam: 27.0%	**Proportion of deviant users per BZD:* Oxazepam: 0.4% Clonazepam: 0.3% Diazepam: 0.3% Zolpidem: 0.3% Bromazepam: 0.3% Lormetazepam: 0.2% Clorazepate: 0.2% Alprazolam: 0.2% Lorazepam: 0.2% Zopiclone: 0.1% Prazepam: 0.04% Tetrazepam: 0.03% Nordazepam: 0.03%	**BZDs with DSI≥1%:* rate of <1% does not constitute a signal for abuse (12 months) Clonazepam: 2.6% Zolpidem: 2.5% Oxazepam: 2.3% Diazepam: 2.2% Alprazolam: 1.7% Bromazepam: 1.7% Lormetazepam: 1.5% Lorazepam: 1.3% Clorazepate: 1.1% Zopiclone: 1.1%

Pauly[31] 2012 France (2006-2008)	Compare doctor shopping indicator (DSI) across 14 BZDs and 10 opioids [prescribed for analgesic or opioid maintenance treatment (OMT)].	**A) Cohort** (N not reported): inclusion/exclusion criteria not specified.	*1) DSI:* proportion of total drug dispensed obtained by DSQ (DSQ: amount of excess drug obtained by overlapping prescriptions from ≥2 prescribers) (time period not reported). DSI <1% is not a signal for abuse. *Drug with highest DSI:* Buprenorphine (OMT): 12.5%	**Other drugs with DSI≥1%* (time period not reported) Opioid (OMT): 7.2% Morphine: 6.2% Buprenorphine (analgesic): 3.9% Methadone: 3.3% BZD: 1.9% Oxycodone: 1.9%	*BZDs are prescribed at a high rate but have a low rate of abuse/diversion. *Opioids (OMT) prescribed at low rate but have a high level of abuse/diversion.
Pearson[32] 2006 US (1988-1995)	Examine impact of the triplicate prescription program (TPP) on potentially problematic BZD use by race.	**A) Entire cohort** (N=124,867): ≥19 years; Medicaid enrollee for ≥10 out of 12 months prior to TPP; dispensed ≥1 BZDs. (*B+C+D+E)* Cohort stratified by predominant racial neighborhood composition **B) White** (N=45,222) **C) Mixed** (N=43,520) **D) Black** (N=12,054) **E) Hispanic** (N=24,071)	*1) Pharmacy hoppers:* dispensed same BZD from ≥2 pharmacies (7 days) **A)** 1.6% (n=1,955) **B)** 1.3% (n=588) **C)** 1.7% (n=740) **D)** 1.4% (n=169) **E)** 1.9% (n=458) *2) Problematic use of BZD:* BZD use was >2 times MRDD OR duration of BZD treatment >120 days **A)** 40.2% (n=50,197) *3) Any potentially problematic BZD use:* (1 or 2) pharmacy hopper or problematic use of BZD **A)** 42.8% (n=53,444) **B)** 51.6% (n=23,335) **C)** 41.1% (n=17,887) **D)** 34.5% (n=4,159) **E)** 33.7% (n=8,112)	*After introduction of TPP there was a sudden and sustained reduction in BZD use and potentially problematic use in all New York neighborhoods. *Across all practices and pharmacy locations black enrollees were most likely, white enrollees least likely, to experience reductions in access to BZDs. *'>83%' of baseline pharmacy hoppers discontinued post-TPP.	
Peirce[33] 2012 US	Compare doctor and pharmacy shopping	**A) "Living" persons cohort** (N=1,049,205): ≥18 years; dispensed ≥1	*1) Pharmacy shopper*: ≥4 dispensing pharmacies (6 months) **A)** 1.3% (n=13,619)	**Pharmacy shoppers (entire cohort) with ≥4 prescriptions dispensed* (6 months)	*86% of decedent cohort deaths were due to a controlled substance.

(Jul 2005-2007)	behaviors between deceased and living persons, and identify factors that predict a drug-related death (controlled substances).	schedule II-IV controlled substance between Jul 2005-Dec 2007. **B) Decedent cohort** (N=698): *A)* and death recorded as drug-related by the medical examiner in the Forensic Drug Database. **C) Entire cohort** (N=1,049,903): *A) + B)*	**B)** 17.5% (n=122) **C)** 1.3% (n=13,741) •*In pharmacy shoppers (entire cohort), proportion of doctor shoppers* (6 months) 55.6% (n=7,640) *2) Doctor shopper*: ≥4 prescribers (6 months) **A)** 3.6% (n=37,594) **B)** 25.2% (n=176) **C)** 3.6% (n=37,770) •*In doctor shoppers (entire cohort), proportion of pharmacy shoppers* (6 months) 20.2% (n=7,640)	90.0% (n=12,361) **Pharmacy shoppers (entire cohort) with ≥3 controlled substances dispensed* (6 months) 50.3% (n=6,918) **Doctor shoppers with ≥4 prescriptions dispensed* (6 months) 82.6% (n=31,180) **Doctor shoppers (entire cohort) with ≥3 controlled substances dispensed* (6 months) Doctor shopper: 49.2% (n=18,566)	*Predictors of drug-related death: greater number of prescriptions dispensed (not defined, OR 1.14); dispensed an opioid (OR 3.40); dispensed a BZD (OR 7.21); dispensed both BZD and opioid (OR 14.92); pharmacy and doctor shopper (OR 3.59); pharmacy shopper alone (OR 3.8); doctor shopper alone (OR 2.03). *Older age (not defined) was less associated with drug-related death (OR 0.96).
Pradel[34] 2004 France (Sep 1999-Dec 2000)	Assess rates of doctor shopping for high dosage buprenorphine (HDB) maintenance therapy (opioid)	**A) Cohort** (N=2,587): ≥1 HDB dispensings; >31 days of follow up. Excluded if: insufficient number of prescriptions.	*1) Doctor shopper:* overlapping prescriptions and ≥2 prescribers (16 months) **A)** 39.5% (n=1,023) •*In doctor shoppers: persons dispensed ≥16 mg per day of HDB (16 months)* 8.5% (n=87)	**Quantity HDB obtained by doctor shoppers:* 18.7% (1,802,806 mg) **Delivered doses of HDB for doctor shoppers (mg/day):* 2.2 mg	
Pradel[35] 2009 France (2000, 2002, 2004, 2005)	Assess the prevalence of doctor shopping for HDB (opioid) and evaluate the impact of the prescription monitoring program (PMP)	**A) Cohort** (N=21,911): ≥2 HDB dispensings in 35 days.	*1) Doctor shopping quantity (DSQ)*: amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months). Range: 631 (2000) to 1151 (2004) grams *2) Doctor shopping indicator (DSI):* proportion of total drug dispensed obtained by DSQ (12 months) Range: 14.9% (2000) to 21.7% (2004)	**Impact of PMP (last 6 months of 2004 to last 6 months of 2005):* *DSQ*: 1151 grams to 858 grams. *DSI*: 21.7% to 16.9%. *At any given time period, approximately 200 patients ('<8%') obtained 80% of HDB.	

	for maintenance treatment.			*75% of users did not have a DSQ.	
Pradel[36] 2010 France (2003)	Assess abuse potential of eight BZDs (14 formulations) via doctor shopping.	**A) Cohort** (N=128,230): ≥1 BZD dispensings.	*1) Doctor shopping quantity (DSQ)*: amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months). Total BZD DSQ: 361,428 DDD *BZD with highest DSQ:* Flunitrazepam 1 mg: 108,727 DDD *2) Doctor shopping indicator (DSI):* proportion of total drug dispensed obtained by DSQ. DSI<1% does not constitute a signal for abuse (12 months) *BZD with highest DSI:* Flunitrazepam 1 mg: 42.8%	**Volume of drug obtained by DSQ (DDD)* (12 months) Bromazepam 6 mg: 56,913 Clorazepate 50 mg: 36,335 Alprazolam 0.5 mg: 14,852 Diazepam 10 mg: 11,125 Lorazepam 2.5 mg: 10,360 Clonazepam 2 mg: 7,752 Lorazepam 1 mg: 4,222 Tetrazepam 50 mg: 2,910 Clorazepate 10 mg: 2,645 Alprazolam 0.25 mg: 1,308 Diazepam 5 mg: 1,110 Clorazepate 5 mg: 401 Diazepam 1 mg: 200 **Drugs with DSI ≥1%* (12 months) Diazepam 10 mg: 3.2% Clorazepate 50 mg: 2.7% Alprazolam 0.5 mg: 1.9% Bromazepam 6 mg: 1.9% Clonazepam 2 mg: 1.8% Lorazepam 2.5 mg: 1.1%	*For BZDs with multiple formulations, highest doses always had higher DSI/DSQ than lower doses. *BZDs by abuse potential: Very high: flunitrazepam 1 mg; High: diazepam 10 mg, clorazepate 50 mg; Intermediate: alprazolam 0.5 mg, bromazepam 6 mg, clonazepam 2 mg; Low: alprazolam 0.25 mg; clorazepate 5-10 mg; diazepam 1-5 mg; lorazepam 1-2.5 mg; tetrazepam 50 mg.
Rice[37] 2012 US (2007-2009)	Identify user characteristics and behavior associated with diagnosed opioid abuse.	**Cohort** (N=821,916): aged 12-64 years; ≥1 opioid dispensings; continuously eligible in 12 months prior to index date. Cohort stratified by opioid abuse diagnosis.	*1) ≥1 early refills:* prescription opioid refill occurred with >25% of the days' supply remaining on the previous prescription for the same active ingredient (12 months) **A)** 38.4% (n=2,449) **B)** 4.1% (n=33,343)	**Mean (SD) dispensing pharmacies* (12 months) **A)** 2.4 (2.3) **B)** 0.7 (0.9) **Mean (SD) prescribers* (12 months) **A)** 3.2 (3.5) **B)** 0.8 (1.3)	*Abusers more likely to have filled opioid prescriptions previously (IR or ER). *Predictors of 'abusers': 1-5 prior opioid prescriptions (OR 2.23); 6 prior opioid prescriptions (OR 6.85); ≥1

		A) Abusers (N=6,380): ICD-9-CM code related to opioid dependence or poisoning in patient history **B) All other individuals** (N=815,536)		**Mean (SD) prescriptions* (12 months) **A)** 13.3 (13.1) **B)** 1.9 (4.5) **Mean (SD) opioids prescribed* (12 months) **A)** 3.7 (3.7) **B)** 0.9 (1.4) **Mean (SD) active ingredients consumed in opioid prescriptions* (12 months) **A)** 1.9 (1.3) **B)** 0.7 (0.9) *Prior use of propoxyphene (OR 0.73) or hydrocodone (OR 0.70) associated with a reduced probability of abuse when controlling for other factors.	prior prescription for buprenorphine (OR 51.75) or methadone (OR 2.97); ≥1 diagnosis of non-opioid drug abuse (OR 9.89), mental illness (OR 2.45) or hepatitis (OR 2.36); family member diagnosis with opioid abuse (OR 3.01). *The finding that abusers were more likely to receive prescriptions from multiple providers was not significant when controlling for other factors.
Ross-Degnan[38] 2004 US (1988-1990)	Evaluate the impact of a triplicate prescription program (TPP) on problematic and non-problematic BZD use and on use of potential substitute drugs.	**Cohort:** ≥19 years; reside in New York or New Jersey; continuously enrolled in Medicaid for ≥10 out of 12 months for 1988-1990; ≥1 BZD dispensings. Excluded if: reside in nursing home for >1 month. **A) Baseline New York** (N=25,399) **B) Baseline New Jersey**	*1) BZD treatment (>120 days)* **A)** 40.3% (n=10,236) **C)** 41.9% (n=4,579) **B)** 37.5% (n=10,073) **D)** 40.1% (n=10,793) *2) Excessive dose:* average daily dose >2 times MRDD (Various) **A)** 6.7% (n=1,702) **C)** 9.2% (n=1,006) **B)** 7.2% (n=1,934) **D)** 6.2% (n=1,669) *3) Concurrent use of 2 LA BZD in same class* (120 days) **A)** 1.8% (n=458) **C)** 1.1% (n=121) **B)** 1.2% (n=323) **D)** 1.0% (n=270) *4) Concurrent use of 2 SA BZD in same class* (120 days)	**Continuous use (>330 days) and no seizure or panic diagnosis* (Various) **A)** 16.2% (n=41,15) **C)** 15.7% (n=1,716) **B)** 13.7% (n=3,680) **D)** 16.9% (n=4,549) **Existence of any 'problematic' behavior:* outcome measures 1-6 and continuous use (>330 days) and no seizure or panic diagnoses (Various)	*Pharmacy hopping greatly reduced in New York with a similar reduction for both potentially problematic and non-problematic BZD use. *The TPP appears to have encouraged deliberate discontinuation of BZD therapy rather than reducing problems in use. *More people in New York who used BZDs appropriately were

		(N=26,860) **C) Post-TPP implementation New York** (N=10,928) **D) Post-TPP New Jersey** (N=26,914): TPP was not implemented in New Jersey. MRDD: 10 DME/day >65 years; 20 DME/day for <65 years.	**A)** 3.7% (n=940) **C)** 2.5% (n=274) **B)** 4.2% (n=1,129) **D)** 4.5% (n=1,212) *5) Receipt of ≥4 different BZDs* (120 days) **A)** 1.7% (n=432) **C)** 0.6% (n=66) **B)** 1.9% (n=511) **D)** 1.9% (n=512) *6) Pharmacy hopping:* dispensed same BZD from ≥2 pharmacies (7 days) **A)** 7.7% (n=1,956) **C)** 3.7% (n=405) **B)** 3.8% (n=1,090) **D)** 3.9% (n=1,050) *7) Receipt of a long half-life BZD for person aged >65 years* (Various) **A)** 56.1% (n unclear) **C)** 51.3% (n unclear) **B)** 52.6% (n unclear) **D)** 48.6% (n unclear)	**A)** 42.8% (n=10,871) **C)** 45.1% (n=4,929) **B)** 40.1% (n=10,771) **D)** 42.0% (n=11,304) *After TPP, there was a sudden and sustained reduction in BZD use in New York (-54.8%), with no changes in New Jersey.	affected by the policy, i.e. young AFDC women (Aid to Families with Dependent Children), living in low-income areas or high minority areas.
Rouby[39] 2012 France (2005)	Assess the extent of tianeptine abuse compared to other antidepressants (ADs) and BZDs/Z-drugs.	**A) AD cohort** (N=410,525): ≥1 AD dispensings. **B) BZD/Z-drug cohort** (N=663,107): ≥1 BZD/Z-drug dispensings.	*1) Doctor shopping quantity (DSQ)*: amount of excess drug dispensed by overlapping prescriptions written by ≥2 prescribers (12 months). *Drug with highest DSQ:* **A)** Tianeptine: 96,183 DDD **B)** Zolpidem: 499,010 DDD *2) Doctor shopping indicator (DSI):* proportion of total drug dispensed, obtained by DSQ (12 months). DSI ≥1% is a signal for abuse. *Drug with highest DSI:* **A)** Tianeptine: 2.0% **B)** Flunitrazepam: 30.2%	**Volume of drug obtained via DSQ (DDD)* (12 months) **A)** Paroxetine: 58,738 Fluoxetine: 52,383 Venlafaxine: 36,483 Mianserin: 15,344 Amitriptyline: 12,102 Mirtazapine: 10,285 Milnacipran: 4,417 **B)** Flunitrazepam: 436,647 Bromazepam: 379,785 Oxazepam: 109,239 Clonazepam: 59,996 Diazepam: 47,339	**Drugs with DSI≥1%* (12 months) **A)** Mianserin 1.0% **B)** Clonazepam: 3.0% Zolpidem: 2.2% Oxazepam: 2.1% Diazepam: 2.0% Bromazepam: 2.0%
Seal[40] 2012 US (Oct 2005-Dec 2010)	Investigate the effect of mental health disorders on risk of adverse clinical outcomes	**Cohort** (N=141,209): Iraq or Afghanistan veteran who entered VA database between Oct 2005-Dec 2008; within 12 months of entry	*1) ≥1 early refill:* obtaining the same opioid prescription >7 days before the end of the previous prescription (12 months) **A)** 20.4% (n=914) **B)** 33.8% (n=2,701)	**Adverse clinical outcomes for opioid users* (12 months) *i) Opioid-related accidents and overdoses:* **A)** 0.02% (n=1) **B)** 0.4% (n=29)	

	associated with high use of prescription opioids.	received a non-cancer pain diagnosis (ICD-9-CM code); ≥1 opioid dispensings for ≥20 consecutive days. Stratified by mental health diagnosis (ICD-9-CM code). **A) No mental health diagnosis** (n=4,488) **B) Mental health diagnosis including PTSD** (n=7,983) **C) Mental health diagnosis excluding PTSD** (n=3,205) **D) Entire cohort** (N=15,676): *A) + B) + C)*	**C)** 30.6% (n=980) **D)** 29.3% (n=4,595) *2) Highest quintile for opioid dose* (12 months) **A)** 15.9% (n=712) **B)** 22.7% (n=1,813) **C)** 19.2% (n=615) **D)** 20.0% (n=3,140) *3) Concurrent use of ≥2 types of opioids:* >7 days of overlap (30 days) **A)** 10.7% (n=478) **B)** 19.8% (n=1,581) **C)** 17.3% (n=553) **D)** 16.7% (n=2,612) *4) Concurrent use of ≥2 types of sedative hypnotics:* >7 days of overlap (30 days) **A)** 7.6% (n=343) **B)** 40.7% (n=3,251) **C)** 25.0% (n=802) **D)** 28.0% (n=4,396) *5) Median duration of opioid use ≥2 months* (12 months) **A)** 42.7% (n=1,916) **B)** 63.2% (n=5,047) **C)** 57.0% (n=1,828) **D)** 56.1% (n=8,791)	**C)** 0.2% (n=7) **D)** 0.2% (n=37) *Prevalence of all adverse clinical outcomes (wounding, alcohol injury, self-inflicted injury or violence) was greater for those prescribed an opioid. *Veterans with a mental health diagnosis were more likely to receive an opioid for pain than persons without a mental health diagnosis, and likelihood increased if the diagnosis included PTSD. *Veterans with PTSD were more likely to receive a sedative.	
Simoni-Wastila[41] 2004 US (1988-1990, 1995)	Assess the effect of New York triplicate prescription program (TPP) on changes in BZD and other	**A) New York** (N=6,054): reside in New York; ≥19 years; continuously enrolled in Medicaid for ≥10 out of 12 months for 1988-1990 and 1995; ≥1 inpatient or ≥2	*1) Probably problematic behavior:* dispensed same BZD from ≥2 pharmacies (7 days) OR BZD use >2 times MRDD (time period not reported) Rate in 1988 to 1990 rates [% change] **A)** 7.1 to 2.4 [-4.7%]	*Probably non-problematic BZD use (BZD use of ≤120 days, no pharmacy hopping or high daily dose) was affected to a greater extent by TPP then problematic BZD use.	*6 months post-TPP, anxiolytic use increased 85.7% in New York, sedative-hypnotic use increased 35.0%. There were no changes in utilization for BZDs in New

	psychoactive drug use compared to New Jersey (no TPP).	outpatient diagnoses of a specified mood disorder in 1988. **B) New Jersey** (N=6,875): *A)* but reside in New Jersey.	**B)** 4.0 to 3.4 [-0.6%]	*The implementation of the TPP resulted in abrupt, large and sustained reductions in BZD use among chronically ill users in New York relative to identically defined users in New Jersey who were not exposed to TPP.	Jersey. *Reduction in BZD use was sustained 7 years after TPP.
Skurtveit[42] 2011 Norway (2005-2008)	Determine prevalence of persistent/ problematic opioid use.	**A) Cohort** (N=245,006): ≥1 dispensings of a weak opioid (codeine, tramadol or dextropropoxyphene). Excluded if: received any opioid for palliative treatment of malignant disease. Strong opioids: buprenorphine, fentanyl, hydromorphone, ketobemidone, morphine, oxycodone, pentazocine and pethidine.	*1) Persistent user*: dispensed ≥1 opioid (not further specified) each year from 2005 to 2008; in 2008 dispensed >365 DDD of opioids in 2008 (48 months) **A)** 0.3% (n=686) *2) Milder probable problematic user indicator:* dispensed ≥1 opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed >365 DDD of opioids and ≥4 prescribers (48 months) **A)** 0.2% (n=421) *3) Probable problematic user*: dispensed ≥1 opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed >365 DDD of opioids; ≥4 prescribers and >100 DDD of BZDs (48 months) **A)** 0.08% (n=191) *4) Stricter probable problematic user indicator:* dispensed ≥1 opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed >365 DDD of opioids; ≥4 prescribers and >300 DDD of BZDs (48 months) **A)** 0.06% (n=139) *5) Strictest probable problematic user*	*9.5% of codeine users, 21.0% of tramadol users, and 22.3% of dextropropoxyphene users (in 2008) were dispensed a LA opioid as their first opioid in 2005.	

			indicator: dispensed ≥1 opioid (weak or strong) in each year from 2005 to 2008; in 2008 dispensed >365 DDD of opioids; ≥7 prescribers and >100 DDD of BZDs (48 months) **A)** 0.05% (n=126)		
Soumerai[43] 2003 US (1987-1990)	Determine if pharmacy hopping is associated with dose escalation in long term BZD users (≥2 years) and identify predictors of dose escalation.	**A) Entire cohort** (N=2,440): ≥2 years of BZD use; enrolled in Medicaid for ≥10 out of 12 months per year 1987-1990. (*B + C)* **B) Continuing BZD user** (N=1,980) *A)* but ≥2 years of BZD use between 1988-1990. **C) Incident BZD user** (N=460): *A)* but no BZD use before Dec 1987.	*1) Pharmacy hoppers:* dispensed same BZD from ≥2 pharmacies (7 days) **A)** 7.4% (n=180) **B)** 7.0% (n=139) **C)** 8.9% (n=41) *2) Users escalated to 'high' dosages:* 20 (elderly patients) or 40 (younger patients) diazepam milligram equivalents per day (24 months) **A)** 1.6% (n=40) **B)** 1.3% (n=26) **C)** 3.0% (n=14)	*Predictors of dose escalation: **B+C)** regular use of SA, high potency BZD lorazepam; or young users (<45 years). **B)** Use of antidepressants and pharmacy hopping (OR 5.2). *Long-term use of BZDs is not associated with notable dose escalation.	
Sullivan[44] 2010 US (2000-2005)	Validate an indicator of opioid misuse and determine the demographic, clinical, and pharmacological risks associated with opioid misuse.	**A) Commercially insured** (N=21,685): ≥18 years; chronic opioid user, i.e. ≥90 days of opioid use in any 6 month period between Jan 2001-Dec 2004; continuous enrolment 12 months prior to and post index date (first opioid dispensing); identified in HealthCore dataset. Excluded if: ≥32 day gap in opioid use;	*1) Opioid misuse score:* based on excess days supplied short- and long-acting opioids, number of dispensing pharmacies and prescribers (6 months). Score 0-1: no misuse **A)** 70.0% (n=15,180) **B)** 76.0% (n=7,721) Score 2-4: possible misuse **A)** 24.0% (n=5,205) **B)** 20.0% (n=2,032) Score ≥5: probable misuse **A)** 6.0% (n=1,302) **B)** 3.0% (n=305)	*For commercially insured cohort, risk of diagnosis of opioid abuse increased 41% for every 1 point increase in opioid misuse score. *For publically insured cohort, risk of diagnosis of opioid abuse increased 51% for every 1 point increase in opioid misuse score. *Factors that increase risk of opioid misuse: younger age, back pain, multiple pain complaints, substance abuse	

		cancer diagnosis within 12 months of index date (pre- or post-); resident of nursing home or hospice user. **B) Publically insured** (N=10,159): *A)* but identified in Arkansas Medicaid.		disorder, high daily dose of opioids (>120 mg MED/day) and shorting acting schedule II opioids.	
Thirion[45] 2002 France (Sep-Dec 1999)	Identify and profile deviant users dispensed buprenorphine (opioid).	**A) Cohort** (N=2,078): ≥1 buprenorphine dispensings.	*1) Deviant:* ≥3 prescribers or dispensed >20 mg/day of buprenorphine (4 months) **A)** 18.1% (n=377)	**Number of prescribers* (4 months) 1 prescriber: 66% (n=1,371) 2 prescribers: 22% (n=457) 3-5 prescribers: 11% (n=229) ≥6 prescribers: 1% (n=21)	**Deviant group profile:* younger, male and higher consumption of BZDs. **Mean (SD) prescriptions* (4 months) Deviant user: 10.1 (5.9)
Victorri-Vigneau[46] 2006 France (second half of years 2001, 2002 and 2003)	Demonstrate impact of intervention program to reduce excessive doses of psychotropic drugs (medicine class not further specified).	**A) Intervention cohort** (N=1,390) reside in Pays de Loire; dispensed >2 times maximum recommended daily dose (MRDD) for ≥3 consecutive months for one psychotropic drug. *(Includes but is not limited to cohorts B and C.)* **B) No action cohort** (N=422): *A)* and reimbursement code related to "serious problems of behavior and personality". **C) Action cohort**	Proportion of cohort pre-intervention to post-intervention *1) >2 times MRDD* (3 consecutive months) **A)** 100% (n=1,390) to 89.5% (n=1,244) **B)** Figures not reported (reduction of 58.5% of patients meeting this criteria) **C)** Figures not reported (reduction of 66% of patients meeting this criteria) **D)** Figures not reported (reduction of 46.2% of patients meeting this criteria) *2) Excess consumption*: average daily consumption exceeds MRDD specified in drug monograph (change from pre- to post-intervention) (12 months) **A)** Not reported **B)** 2.5 to 2.1 [-15%] **C)** 2.6 to 1.9 [-27%] **D)** 2.3 to 2.1 [-9%]	**Mean number of prescribers* (12 months) [% change] **B)** Mean not reported [-4%] **C)** 2.67 to 2.28 [-15%] **D)** Mean not reported [2%] (direction of change not reported) **R ratio:* number of patients receiving >2 MRDD of psychotropic medicine to number of patients receiving psychotropic medicine **C)** 100% (n=840) to 33.4% (n=281). *When considering all persons dispensed psychotropic medicine, the R ratio decreased by 14.1%	*Health professionals involved with 'action cohort' filed 116 drug addiction reports. The prevalence of medicines mentioned in these reports: Zopiclone: 19% Zolpidem: 17% Oxazepam: 16% BZD (other): 13% Meprobamate: 11% Clorazepate: 9% Buprenorphine: 8% Bromazepam: 7%

		(N=840): *A)*; doctors and pharmacists of identified users received a letter to review their patients' medical prescriptions. Excluded if: assigned to *B)*; refusal to have data included in study; death, or moved residence. **D) Comparison cohort** (N not reported): *A)* but reside in Vendee.		over the study period.	
Victorri-Vigneau[47] 2011 France (Jul-Dec 2005)	Characterize AD over-consumption.	**A) Tianeptine** (N=7,264): ≥2 tianeptine dispensings. [MRDD = 37.5 mg] **B) Milnacipran** (N=1,918): ≥2 milnacipran dispensings. [MRDD = 100 mg]	*1) Overconsumer:* dispensed more medicine than medically required (6 months) **A)** Dispensed 1.7 times the MRDD: 0.4% (n=29) **B)** Dispensed 2 times the MRDD: 2.4% (n=46) *2) Pharmacy shoppers:* ≥4 dispensing pharmacies (6 months) •*In tianeptine overconsumers (n=29)*: 20.7% (n=6) •*Other tianeptine users (n=7,235)*: 1.0% (n=72) •*Milnacipran overconsumers (n=46):* 4.3% (n=2) •*Other milnacipran users (n=1,872):* 1.4% (n=26) *3) % R ratio>1:* observed number of dispensings delivered to the user is greater than the amount actually required (6 months)	**Median (range) prescribing physicians* (6 months) **A)** 1 (1-6) **B)** 1 (1-5) **Median (range) dispensing pharmacies* (6 months) **A)** 1 (1-13) **B)** 1 (1-6) **Median (range) dispensings* (6 months) **A)** 5 (2-40) **B)** 4 (2-17) **Consumption factor >1:* estimate of average daily consumption of a psychotropic drug divided by the MRDD (6 months) **A)** 17.2% (n=125) **B)** 32.3% (n=620)	*The consumption factor reached higher values for tianeptine (up to 11 times higher) but occurred less frequently compared to milnacipran. *Pharmacy shopping increased risk of overconsumption for tianeptine (OR 10.78).

			•*Tianeptine overconsumers:* 89.7% (n=26) •*Other tianeptine user:* 27.9% (n=2,015) •*Milnacipran overconsumers:* 93.5% (n=43) •*Other milnacipran users:* 29.9% (n=560)		
Victorri-Vigneau[48] 2013 France (Feb-Jul 2010)	Identify and characterize zolpidem and zopiclone (Z-drugs) users.	**A) Zopiclone** (N=21,860): ≥1 zopiclone dispensings; number of dispensings are equal to or higher than medically required rate (3.75 mg). **B) Zolpidem** (N=25,168): ≥1 zolpidem dispensings; number of dispensings are equal to or higher than medically required rate (5 mg).	*1) Problematic user*: latent class analysis based on: prescribing physician type, doctor shopping, pharmacy shopping, excess use, agreement with practice guidelines and associated psychiatric disorders (6 months) **A)** 0% (n=0) **B)** 1.0% (n=252) *2) Doctor shopper:* ≥4 prescribers (6 months) **A)** 1.1% (n=241) •*In problematic zopiclone users:* 0% (n=0) **B)** 1.0% (n=252) •*In problematic zolpidem users:* 47.2% (n=119) *3) Pharmacy shopper:* ≥4 dispensing pharmacies (6 months) **A)** 1.7% (n=372) •*In problematic zopiclone users:* 0% (n=0) **B)** 2.1% (n=529) •*In problematic zolpidem users:* 84.1% (n=212) *4) Excess use*: medication possession ratio (MPR) >1: number of medicine supply days excluding last refill divided by the number of days between the first and last dispensing (6 months) **A)** 32.8% (n=7,171)	**Problematic users mean (SD) daily dose (mg/day)* (6 months) **A)** 0 (0) **B)** 20.9 (2.4) *Zolpidem 'problematic' users were younger, average daily dose was higher and the number of dispensings is 2-fold higher.	

			•*In problematic zopiclone users:* 0% (n=0) **B)** 31.2% (n=7,853) •*In problematic zolpidem users:* 75.0% (n=189)		
Wainstein[49] 2011 France (Jan-Jun 2008)	Characterize consumption behavior related to three psychotropic drugs (BZD, Z-drugs and AD).	**A) Bromazepam** (N=40,644): ≥18 years; ≥2 bromazepam dispensings. [MRDD = 18 mg]. **B) Zolpidem** (N=36,264) ≥18 years; ≥2 zolpidem dispensings. [MRDD = 10 mg]. **C) Paroxetine** (N=31,235): ≥18 years; ≥2 paroxetine dispensings. [MRDD = 40 mg]. Excluded if: 2 dispensings received on the same day.	*1) Problematic user:* latent class analysis based on excessive medicine use, prescribing physician specialty, 'doctor shopping' behavior, 'pharmacy shopping' behavior, prescription in agreement with practice guidelines (6 months) **A)** 1.0% (n=407) **B)** 1.0% (n=363) **C)** 0% (n=0) *2) Pharmacy shoppers:* ≥4 dispensing pharmacies (6 months) **A)** 1.2% (n=488) •*In problematic bromazepam users:* 93.1% (n=379) **B)** Not reported • *In problematic zolpidem users*: 65.0% (inferred from graph) (n=236) **C)** Not reported • *In problematic paroxetine users:* 0% *3) Doctor shoppers:* ≥4 prescribers doctors (6 months) **A)** 0.4% (n=163) • *In problematic bromazepam users:* 41.0% (n=167) **B)** Not reported • *In problematic zolpidem users:* 32% (inferred from graph) (n=117) **C)** Not reported • *In problematic paroxetine users:* 0%		

			4) Estimate of average daily consumption of a psychotropic medicine greater than MRDD (6 months) **A)** 1.1% (n=448) • *In problematic bromazepam users:* 56.0% (n=228) **B)** 17.8% (n=6,455) •*In problematic zolpidem users:* 89.0% (inferred from graph) (n=324) **C)** 0.3% (n=94) •*In problematic paroxetine users:* 0% (n=0)		
White[50] 2009 US (2005-2006)	Assess feasibility of using medical and prescription drug claims to develop models that identify prescription opioid abuse or misuse.	Model A cohort details. **A) Cohort** (N=116,382): aged 12-64, ≥1 opioid claim and ≥1 medical claim. *(B + C)* **B) Abusers** (N=875): *A)* ICD-9-CM code of opioid dependence or poisoning **C) All other individuals** (N=115,507): *A)* not *B)* Model B cohort details **D) Cohort (subset of A)** (N=8,592): *A)* claims occurred Sep-Dec 2006. *(E + F)* **E) Abusers** (N=303): *B)* between Sep-Dec 2006. **F) All other individuals** (N=8,289): *C)* not *E)*.	*1) Number of prescribers:* ≥2 prescribers (3 months) **A)** not analyzed: **D)** 26.1% (n=2,242) **B)** not analyzed: **E)** 40.9% (n=124) **C)** not analyzed: **F)** 25.6% (n=2,118) *2) Pharmacy shopper:* ≥2 dispensing pharmacies (3 months) **A)** 7.9% (n=9,213): **D)** 19.9% (n=1,708) **B)** 39.4% (n=345): **E)** 38.0% (n=115) **C)** 7.7% (n=8,868): **F)** 19.2% (n=1,593) *3) ≥4 opioid prescriptions* (3 months) **A)** 10.1% (n=11,740): **D)** not analyzed **B)** 60.1% (n=526): **E)** not analyzed **C)** 9.7% (n=11,214): **F)** not analyzed *4) ≥1 early refills of opioid prescriptions:* two consecutive opioid prescriptions where days of supply of first prescription was >10% higher than the number of days between prescriptions (3 months) **A)** 4.0% (n=4,615): **D)** 16.5% (n=1,414) **B)** 36.0% (n=315): **E)** 40.9% (n=124)	*Factors associated with ICD code of opioid abuse, dependence or poisoning (not related to an outcome measure defining misuse): male (OR 2.19), ≥3 dispensing pharmacies (OR 1.96), ≥1 early refills of opioid prescriptions (OR 6.52), ≥2 consecutive months of dose escalation (OR 1.59), ≥12 opioid prescriptions (OR 2.12), ≥1 non-opioid substance abuse diagnosis (OR 5.83).	

			C) 3.7% (n=4,300): **F)** 15.6% (n=1,290) *5) Dose escalation:* 50% increase in the mean milligrams of morphine per month for 2 consecutive months (3 months) **A)** 0.4% (n=509): **D)** not analyzed **B)** 4.7% (n=41): **E)** not analyzed **C)** 0.4% (n=468): **F)** not analyzed		
Wilsey[51] 2010 US (2007)	Determine prevalence and predictors of multiple provider episodes (MPEs) for different controlled substances.	**A) Cohort** (N not reported): prescription for schedule II-IV controlled substances. Excluded if: missing or incomplete user or provider identification; implausible prescriptions; use of medications not suggestive of standard delivery systems employed by most users. Prescription level data (N=27,773,347)	*1) <u>Prescriptions</u> obtained by multiple provider episodes (MPEs):* ≥2 prescribers and ≥2 dispensing pharmacies (30 days) **A)** 8.4% (n prescriptions=2,332,962) *2) Proportion of prescription obtained by MPEs by drug class:* Opioids: 12.8% BZDs: 4.2% Stimulants: 1.4% Anorectics: 0.9%	**Risk of simultaneous MPEs for different controlled substances:* *i) Opioids and:* BZD: OR 15.54 Stimulants/anorectics: OR 10.56 BZD and stimulants/anorectics: OR 21.40 *ii) BZD and:* Opioids: OR 13.04 Stimulants/anorectics: OR 20.60 Stimulants/anorectics and opioids: OR 3.64 *iii) Stimulant and:* BZD: OR 19.62 Opioids: OR 9.23 BZD and opioids: OR 26.83 *iv) Anorectic and:* BZD: OR 9.95 Opioids: OR 11.06 BZD and opioids: OR 27.16	*For opioids: hydromorphone and controlled release oxycodone were most associated with MPEs. *Younger age predictor of MPEs associated with opioid and BZDs. *Older age associated with MPE use to obtain stimulants and anorectics. *Males were more likely to use MPE for BZD; less likely for stimulants; no gender relationship between anorectics or opioids. *Strongest predictor was simultaneously receiving prescriptions for different controlled substances and concurrent use of multiple prescribers to obtain other controlled substances.
Wilsey[52] 2011	Determine if persons	**A) Cohort** (N=12,870,831)	*1) Multiple prescribers:* 2-5 prescribers (12 months)	**Single prescriber* (12 months)	*Persons accessing 2-5 prescribers are different

US (1999-2007)	accessing 2-5 prescribers were distinguishable from persons accessing 1 prescriber in demographic characteristics or opioid utilization (opioid).	Prescribed same schedule II or III opioid in 12 months. Excluded if: missing/incomplete prescription, pharmacy or prescriber information; implausible prescription; use of opioids not suggestive of chronic pain.	**A)** 22.1% (n=2,849,464) *2) Frequency of use of multiple prescribers per drug* (12 months) Hydrocodone (schedule III): 68.3% Codeine (schedule III): 9.8% Oxycodone IR (schedule II): 7.8% Oxycodone ER (schedule II): 3.0% Fentanyl (transcutaneous) (schedule II): 4.0% Morphine ER (schedule II): 3.2% Methadone (schedule II): 1.5% Hydromorphone (schedule II): 1.5% Morphine IR (schedule II): 0.6% Fentanyl (oral transbuccal): 0.1% Meperidine (schedule II): 0.1% Levorphanol (schedule II): 0.02%	**A)** 77.9% (n=10,021,367) *Persons accessing 2-5 prescribers were more likely to use LA opioids than hydrocodone (ranging from 7.8% [fentanyl patch] to 38.8% [methadone]) and less likely to use SA opioids. *Likelihood of MPEs increased with age. *Persons with multiple prescribers were more likely to: be female; reside in a small geographic area.	from those using one prescriber, but differences do not suggest abuse.

[a] See Electronic Supplementary Material 6 for reference list.

[b]Period of observation covers the entire year, unless otherwise stated.

[c]Reported aim(s) and cohort(s) may differ from original article as we only report aspects of paper related to prescription drug misuse.

[d]We renamed/redefined some measures from the original manuscript for clarity and due to space constraints. If either a rate or the number of people identified by a measure was not reported, where possible we calculated it. All reported rates were derived from drug user or misuse cohorts unless otherwise stated.

ACRONYMS:

AD(s): antidepressant(s)
AP: antiparkinson
BMT: buprenorphine maintenance therapy
BZD(s): benzodiazepine(s)
DDD: defined daily dose
DSI: doctor shopping indicator
DSQ: doctor shopping quantity
DZE: diazepam milligram equivalent
ED: emergency department

ER: extended release
GP(s): general practitioner(s)
HDB: high dosage buprenorphine
ICD: International Classification of Diseases
IR: immediate release
LA: long acting
MPE(s): multiple provider/prescriber episode(s)
MRDD: maximum recommended daily dose
OMT: opioid maintenance therapy
OR: odds ratio
PMP: prescription monitoring program
PTSD: Post-Traumatic Stress Disorder
SA: short acting

Electronic Supplementary Material 8 The Reported Extent of Prescription Drug Misuse Based on Indicators with a Defined Threshold

Electronic Supplementary Material 8.1 Proportion of Cohort Identified as 'Misusers' Based on Indicators with a Defined Threshold

A. Stand-alone measures of misuse (drug users only)

Stand-alone measure details (A single behavior of misuse measured in drug users: persons dispensed the drug of interest)	**Time period (days)[a]**	**Drug user cohort[b]**	**Reference[c]**
Number of prescribers			
≥2 prescribers	90	26.1	[50]
2-5 prescribers	365	22.1	[52]
≥3 prescribers	365	NM	[16]
≥4 prescribers	180	0.9	[2]
≥4 prescribers	NR	0.5	[3]
≥4 prescribers	180	3.6	[33]
≥4 prescribers	180	1.1	[48]
≥4 prescribers	180	0.4	[49]
Number of dispensing pharmacies			
≥2 dispensing pharmacies	7	1.9	[32]
≥2 dispensing pharmacies	7	3.9	[38]
≥2 dispensing pharmacies	7	8.9	[43]
≥2 dispensing pharmacies	90	19.9	[50]
≥4 dispensing pharmacies	180	1.3	[2]
≥4 dispensing pharmacies	180	1.3	[33]
≥4 dispensing pharmacies	180	1.4	[47]
≥4 dispensing pharmacies	180	2.1	[48]
≥4 dispensing pharmacies	180	1.2	[49]
Volume of drug dispensed			
≥1 benzodiazepine dispensings per year for 4 consecutive years	1440	2.2	[20]
≥4 dispensings	90	10.1	[50]
>15 defined daily doses of carisoprodol	365	32.2	[3]
≥100 defined daily doses of opioids	365	13.6	[3]
>365 defined daily doses of codeine	365	5.8	[14]
>1000 defined daily doses of carisoprodol	365	0.2	[4]
Daily dose ≥100 morphine milligram equivalent	365	7.8	[23]
Daily consumption of drug greater than maximum recommended daily dose	180	17.8	[49]
>2 times maximum recommended dose	Various	9.2	[38]
≥2 times maximum daily dose	180	2.4	[47]
Number of dispensings greater than medically required	180	29.9	[47]
Overlapping prescriptions or early refills			
≥1 early refills: two consecutive prescriptions for same drug with number of days between prescriptions being >10% lower than number of days' supply in first prescription	365	6.9	[22]
1 early refill: prescription filled >7 days before the end of previous prescription	365	33.8	[40]
≥1 early refills: two consecutive opioid prescriptions where days	90	16.5	[50]

of supply was >10% higher than number of days between prescriptions			
≥1 early refills: prescription opioid refill that occurred with >25% of the days' supply remaining on the previous prescription for the same active ingredient	365	4.1	[37]
≥4 days of overlapping prescriptions	540	11.1	[5]
≥7 days of overlapping prescriptions	365	2.1	[23]
Use of specific prescribed drug			
Long acting or extended release opioids prescribed for acute pain conditions	365	0.1	[23]
Use of ≥4 different benzodiazepines	Various	1.9	[38]
Receipt of long half-life benzodiazepines (persons aged ≥65 years)	NR	51.3	[38]
Duration of treatment			
Median duration of opioid use ≥2 months	365	63.2	[40]
>120 days of benzodiazepine treatment	Various	41.9	[38]
Dose escalation			
Users escalating to 'high' dosages: 20 (elderly patients) or 40 (younger patients) diazepam milligram equivalents per day	NR	3.0	[43]
50% increase in mean milligrams of morphine per month for 2 consecutive months	90	0.4	[50]

[a] All time periods have been converted to days, i.e. 30 days = 1 month; 90 days = 3 months; 180 days = 6 months; 365 days = 12 months etc. NR = not recorded in original manuscript.
[b] If study reported rates for >1 drug user cohort or drug, we record the highest reported rate alone.
[c] See Electronic Supplementary Material 6 for reference list.
NM = no meaningful result was obtained.
NR = not recorded in original manuscript.

B. Composite measures: a single measure of misuse reported in a misuse cohort (where possible, we also record the extent of misuse in a drug user cohort)

Composite measure of misuse details (A single behavior of misuse measured in a defined misuse cohort) *Misuse cohort definition*	**Time period (days)[a]**	**Drug user cohort[b]**	**Misuse cohort[b]**	**Reference[c]**
Number of prescribers				
≥2 prescribers *Misuse cohort definition: ICD-9 code of opioid abuse, dependence or poisoning*	90	26.1	40.9	[50]
≥3 prescribers *≥1 days of overlapping prescriptions*	540	*(0.7)*	5.4	[5]
≥4 prescribers *2 defined daily doses (DDD)/day of carisoprodol; dispensed <100 DDD of opioids, and dispensed <100 DDD of benzodiazepines in 365 days*	NR	0.6	4.5	[3]
≥4 prescribers *Drug-related death*	180	3.6	25.2	[33]
≥4 prescribers *≥4 dispensing pharmacies*	180	*(0.7)*	55.6	[33]
≥4 prescribers *Highest 1% zolpidem users determined by latent class analysis*	180	*(0.5)*	47.2	[48]

≥4 prescribers *Highest 1% bromazepam users determined by latent class analysis*	180	*(0.4)*	41.0	[49]
≥5 prescribers *Pharmaceutical overdose death*	365	N/A	21.4	[18]
Number of dispensing pharmacies				
≥2 dispensing pharmacies *Misuse cohort definition: ≥1 days of overlapping prescriptions*	540	*(2.8)*	21.3	[5]
≥2 dispensing pharmacies *ICD-9 code of opioid abuse, dependence or poisoning*	90	19.9	39.4	[50]
≥3 dispensing pharmacies *≥1 days of overlapping prescriptions*	540	*(0.2)*	1.3	[5]
≥4 dispensing pharmacies *Drug-related death*	180	1.3	17.5	[33]
≥4 dispensing pharmacies *≥4 prescribers*	180	*(0.7)*	20.2	[33]
≥4 dispensing pharmacies *Dispensed 1.7 or 2 times more drug than medically required*	180	1.4	20.7	[47]
≥4 dispensing pharmacies *Highest 1% zolpidem users determined by latent class analysis*	180	*(0.8)*	84.1	[48]
≥4 dispensing pharmacies *Highest 1% bromazepam users determined by latent class analysis*	180	*(0.9)*	93.1	[49]
Volume of drug dispensed				
>2 times maximum recommended daily dose (post-intervention) *Misuse cohort definition: Pre-intervention dispensed >2 times maximum recommended daily dose*	90	N/A	89.5	[46]
≥4 prescriptions *ICD-9 code of opioid abuse, dependence or poisoning*	90	10.1	60.1	[50]
>15 defined daily dose (DDD) of carisoprodol *>365 DDD of codeine*	365	*(1.7)*	30.2	[14]
≥16 mg per day of high dosage buprenorphine *≥2 overlapping prescriptions and ≥2 prescribers*	480	*(3.4)*	8.5	[34]
>100 defined daily dose (DDD) of benzodiazepines *Dispensed >365 DDD of codeine*	365	*(2.9)*	50.5	[14]
>730 defined daily dose (DDD) of codeine *Dispensed >365 DDD of codeine*	365	*(1.1)*	19.0	[14]
Medication possession ratio >1: number of drug supply days excluding last refill divided by the number of days between the first and last dispensing. *Number of dispensings greater than medically required*	180	N/A	32.8	[48]
Number of dispensings greater than medically required *Dispensed 1.7 or 2 times more drug than medically required*	180	29.9	93.5	[47]
Amount of drug dispensed greater than medically required *Highest 1% zolpidem users determined by latent class*	180	*(0.8)*	75.0	[48]

analysis				
Daily consumption of drug greater than medically required *Highest 1% zolpidem users determined by latent class analysis*	180	*(0.9)*	89.0	[49]
Overlapping prescriptions or early refills				
≥1 early refills: two consecutive opioid prescriptions where days of supply was >10% higher than number of days between prescriptions *Misuse cohort definition: ICD-9 code of opioid dependence or poisoning*	90	16.5	40.9	[50]
≥1 early refills: any prescription opioid refill that occurred with >25% of the days' supply remaining on the previous prescription for the same active ingredient *ICD-9 code of opioid dependence or poisoning*	365	4.1	38.4	[37]
Dose escalation				
50% increase in the mean milligrams of morphine in 2 consecutive months *Misuse cohort definition: ICD-9 code of opioid dependence or poisoning*	90	0.4	4.7	[50]

[a] All time periods have been converted to days, i.e. 30 days = 1 month; 90 days = 3 months; 180 days = 6 months; 365 days = 12 months etc. N/A = not applicable as study investigated measure in misuse cohort alone

[b] Where studies report multiple results across drugs or user cohorts we record the highest reported rate. We calculated all bracketed and italicized values. Values were not reported in original manuscript.

[c] See Electronic Supplementary Material 6 for reference list.

C. Composite measures: measure of misuse with two or more behaviors or characteristics reported in drug user and/or misuse cohort(s)

Composite measure details (≥2 behaviors/characteristics of misuse measured in drug user and/or misuse cohorts) *Misuse cohort definition (where applicable)*	**Time period (days)[a]**	**Drug user cohort[b]**	**Misuse cohort[b]**	**Reference[c]**
Composite measures of misuse including number of prescribers and/or number of dispensing pharmacies				
≥2 prescribers and ≥1 days overlapping prescriptions	540	13.9		[5]
≥2 prescribers and ≥1 days overlapping prescriptions	480	39.5		[34]
≥2 dispensing pharmacies in 7 days OR benzodiazepine treatment duration >120 days OR dispensed >2 times maximum recommended daily dose	Various	42.8		[32]
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	540	NR		[6]
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	365	0.9		[8]
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	540	0.7		[9]
≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions	540	0.3		[7]
≥2 dispensing pharmacies within 7 days OR dispensed >2 times maximum recommended daily dose	Various	3.4		[41]

≥3 dispensing pharmacies and ≥1 overlapping prescriptions	540	0.2		[5]
≥3 prescribers and ≥3 dispensing pharmacies	365	1.6		[22]
≥3 prescribers OR dispensed >20 mg/day of buprenorphine	120	18.1		[45]
≥4 prescribers and ≥4 dispensing pharmacies	365	0.5		[22]
≥4 prescribers, ≥1 opioid dispensings for 4 consecutive years and in final year dispensed >365 defined daily doses of opioids	1460	0.2		[42]
≥4 prescribers, ≥1 opioid dispensings for 4 consecutive years, in final year dispensed >365 defined daily doses (DDD) of opioids and >100 DDDs of benzodiazepines	1460	0.08		[42]
≥4 prescribers, ≥1 opioid dispensings for 4 consecutive years, in final year dispensed >365 defined daily doses (DDD) of opioids and >300 DDD of benzodiazepines	1460	0.06		[42]
≥5 prescribers and ≥5 dispensing pharmacies	365	0.2		[22]
≥5 shopping episodes: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions (1 shopping episode)	365	0.07		[8]
≥5 shopping episodes: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions (1 shopping episode)	540	0.1		[9]
≥6 shopping episodes: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions (1 shopping episode) *Misuse cohort definition: ≥2 prescribers, ≥3 dispensing pharmacies and ≥1 days overlapping prescriptions*	540	*(0.03)*	9.5	[7]
≥7 prescribers, ≥1 opioid dispensings for 4 consecutive years, in final year dispensed >365 defined daily doses (DDD) of opioids and >100 DDD of benzodiazepines	1460	0.05		[42]
Opioid misuse score: possible misuse score (score 2-3): based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	14.5		[25]
Opioid misuse score: possible or probable misuse score (score 2-4). Score based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	24.0		[44]
Opioid misuse score: probable misuse score (score ≥4) Score based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	2.2		[25]
Opioid misuse score: probable misuse score (score ≥5) Score based on number of dispensing pharmacies, prescribers, and excess days supplied short- and long-acting opioids	180	6.0		[44]
≥2 letters sent out to physician informing them of patient's problematic use of prescribed drug. Based on alerts of number of prescribers or dispensing pharmacies and/or amount of drug prescribed. *Physician previously sent a letter describing patient's problematic use of prescription drug(s)*	180	N/A	29.8	[21]

Composite measures of misuse including volume of drug dispensed: none of the listed measures include number of prescribers or dispensing pharmacies.				
≥1 opioid dispensings for 4 consecutive years; and in final year dispensed >365 defined daily doses of opioids	1460	0.3		[42]
2 defined daily doses (DDD) per day of carisoprodol, <100 DDD of benzodiazepines and <100 DDD of opioids	365	1.0		[3]
≥100 defined daily doses (DDD) of benzodiazepines and <100 DDD of opioids	365	7.8		[3]
≥2 dispensings of carisoprodol and dispensed: >15 defined daily doses (DDD) of carisoprodol, >2 times recommended maximum daily dose for a period, <100 DDD of opioids and <100 DDD of benzodiazepines	365	1.0		[4]
Dispensed ≥100 defined daily doses (DDD) of benzodiazepines and/or ≥15 DDD of carisoprodol	365	50.1		[1]
Dispensed ≥100 defined daily doses (DDD) of benzodiazepines OR ≥15 DDD of carisoprodol	365	41.9		[1]
Dispensed ≥100 defined daily doses (DDD) of benzodiazepines and ≥15 DDD of carisoprodol	365	8.2		[1]
Dispensed >2 times maximum recommended daily dose OR benzodiazepine treatment duration >120 days	Various	40.2		[32]
Composite measures of misuse including early refills or overlapping prescriptions: none of the measures listed include number of prescribers, dispensing pharmacies or volume of drug dispensed				
Opioid and BZD prescription with ≥7 days overlap	365	1.0		[23]
Concurrent use of 2 long acting benzodiazepines	Various	1.1		[38]
Concurrent use of 2 short acting benzodiazepines	Various	4.5		[38]
≥2 types of concurrent opioid use with >7 days overlap	30	19.8		[40]
≥2 types of concurrent sedative hypnotic use	30	40.7		[40]

[a] All time periods have been converted to days, i.e. 30 days = 1 month; 90 days = 3 months; 180 days = 6 months; 365 days = 12 months etc. N/A = not applicable as study investigated measure in misuse cohort alone. NR = not recorded in original manuscript.

[b] Where studies report multiple results across drugs or user cohorts we record the highest reported rate. We calculated all bracketed and italicized values. Values were not reported in original manuscript.

[c] See Electronic Supplementary Material 6 for reference list.

Electronic Supplementary Material 8.2. Proportion of misusers determined through empirical analysis.

Empirical analysis details (empirically derived thresholds of misuse where relevant)	Time period (days)[a]	Drug user cohort[b]	Reference[c]
Excessive use based on Peaks Over Threshold model	180	7.2	[2]
Highest 1% of carisoprodol users based on Lorenz curve (dispensed ≥480 defined daily doses)	365	1.1	[4]
Highest 10% of codeine users (≥120 defined daily doses)	365	10.7	[1]
Highest quintile (20%) of opioid users	365	22.7	[40]
Cluster analysis based on number of: prescribers; dispensing pharmacies; dispensing episodes and sum of DDD dispensed	270	1.1	[12]
Cluster analysis based on number of: prescribers; dispensing pharmacies; dispensing episodes and sum of DDD dispensed	270	1.1	[13]
Cluster analysis based on number of: prescribers; dispensing pharmacies; dispensing episodes and sum of DDD dispensed	270	6.0	[29]
Cluster analysis based on number of: prescribers; dispensing	270	9.1	[30]

pharmacies; dispensing episodes and sum of DDD dispensed			
Latent class analysis based on gender; age and method of payment	300	0.7	[26]
Highest 1% of drug users based on latent class analysis including consumption factor; prescriber specialty; number of prescribers; number of dispensing pharmacies; consistent with practice guidelines	180	1.0	[49]
Highest 1% of drug users based on latent class analysis including prescriber specialty; number of prescribers; number of dispensing pharmacies; excess use; consistent with practice guidelines; associated psychiatric disorders	180	1.0	[48]

[a] All time periods have been converted to days, i.e. 180 days = 6 months; 365 days = 12 months etc.

[b] Where studies report multiple results across drugs or user cohorts we record the highest reported rate.

[c] See Electronic Supplementary Material 6 for reference list.

Electronic Supplementary Material 9 The Proportion of Prescription Drugs Dispensed to a Misuse Cohort: Determined by a Measure of Misuse with a Defined Threshold

A. Stand-alone and composite measures of misuse reporting the proportion of drugs dispensed to misuser cohorts

Drug class of interest (unit of measurement) *(Misuse cohort definition)*	**Time period (days)[a]**	**Proportion of drug class dispensed to a misuse cohort**	**Reference[b]**
Anorectics *Misuser cohort definition: ≥2 prescribers and ≥2 dispensing pharmacies*	30	0.9	[51]
Benzodiazepines *≥2 prescribers and ≥2 dispensing pharmacies*	7	1.2	[10]
Benzodiazepines *≥2 prescribers and ≥2 dispensing pharmacies*	30	4.2	[51]
Opioids *≥2 prescribers and ≥2 dispensing pharmacies*	7	3.2	[10]
Opioids *≥2 prescribers and ≥2 dispensing pharmacies*	30	9.6	[15]
Opioids *≥2 prescribers and ≥2 dispensing pharmacies*	30	12.8	[51]
Opioids *≥3 prescribers and ≥3 dispensing pharmacies*	365	7.7	[22]
Opioids *≥4 prescribers and ≥4 dispensing pharmacies*	365	3.1	[22]
Opioids *≥5 prescribers and ≥5 dispensing pharmacies*	365	1.5	[22]
Stimulants *≥2 prescribers and ≥2 dispensing pharmacies*	30	1.4	[51]
Prescription drug of interest (unit of measurement) *(Misuse cohort definition)*	**Time period (days)[a]**	**Proportion of drug dispensed to a misuse cohort[c]**	**Reference[b]**
Buprenorphine *Misuse cohort definition: Doctor shopping quantity: amount of excess drug obtained by misusers by overlapping prescriptions from ≥2 prescribers*	485	18.7	[34]
Hydrocodone *≥2 prescribers*	365	68.3	[52]
Hydromorphone *≥2 prescribers and ≥2 dispensing pharmacies*	30	15.2	[15]

[a] All time periods have been converted to days, i.e. 30 days = 1 month; 365 days = 12 months etc.

[b] See Electronic Supplementary Material 6 for reference list.

[c] Per drug class, we report the result of the drug with the highest DSI.

B. Composite measures of misuse reporting the volume of drugs dispensed to misuse cohorts: specific measures of doctor shopping quantity (DSQ) and doctor shopping indicator (DSI)

Drug class or drug of interest	**Time period (days)[a]**	**Measure of misuse: DSQ[b]**	**Measure of misuse: DSI (%)[b]**	**Reference[c]**

Doctor shopping quantity (DSQ): amount of excess drug obtained by misusers by overlapping prescriptions from ≥2 prescribers				
Doctor shopping indicator (DSI) (%)*:* amount of drug calculated by the DSQ, expressed as the proportion of total drug dispensed (i.e. DSQ/total drug volume dispensed). DSI >1% is a signal for drug abuse.				
Drug class				
Benzodiazepines	NR	[d]	1.9	[31]
Benzodiazepines	365	361,428 DDD	NR	[36]
Opioids (OMT)	365	55.3 DDD/1000 population	6.2	[27]
Antidepressants				
Mianserin	365	15,344 DDD	1.0	[39]
Benzodiazepine				
Flunitrazepam	365	[d]	27.0	[30]
Flunitrazepam	365	108,727 DDD	42.8	[36]
Flunitrazepam	365	436,647 DDD	30.2	[39]
Opioids				
Buprenorphine	365	1151 grams	21.7	[35]
Buprenorphine (opioid maintenance therapy)	365	50.3 DDD/1000 population	8.0	[27]
Buprenorphine (opioid maintenance therapy)	NR	[d]	12.5	[31]
Z-drugs				
Zolpidem	365	[d]	2.5	[30]
Zolpidem	365	499,010 DDD	2.2	[39]

[a] All time periods have been converted to days, i.e. 365 days = 12 months etc. NR = not recorded in original manuscript.
[b] Per drug class, we report the result of the drug with the highest DSI.
[c] See Electronic Supplementary Material 6 for reference list.
[d] DSQ not investigated in study

C. Proportion of drug dispensed to empirically defined misuse cohort

Empirical analysis details	**Time period (days)[a]**	**Proportion of drug of interest dispensed to misuse cohort[b]**	**Reference[c]**
Highest 1% of benzodiazepine drug users based on Lorenz curve	365	16.5	[16]
Highest 1% of carisoprodol users	365	18.7	[4]
Highest 1% of biperiden drug users based on Lorenz curve	365	6.2	[16]

[a] All time periods have been converted to days, i.e. 365 days = 12 months etc.
[b] Where studies report multiple results relating to one drug class we report the drug with the highest rate.
[c] See Electronic Supplementary Material 6 for reference list.