Received: 18 June 2021 | Revised: 19 July 2021 | Accepted: 20 July 2021

DOI: 10.1111/bcp.15012

ORIGINAL ARTICLE

Methodological issues in research on drug-related admissions: A meta-epidemiological review with focus on causality assessments

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Funding information
Swedish Network for Pharmacoepidemiology; Swedish state under the agreement between the Swedish government and the county councils (the ALF-agreement), Grant/Award Number: ALFGBG-716941; Swedish Research Council, Grant/Award Number: 2013-02639

Aim: To investigate methodological aspects potentially related to the diverging scientific literature on the prevalence of drug-related hospitalisations, focusing on causality assessments.

Methods: Original studies contributing data to a recent meta-analysis were reviewed. Methodological aspects, in particular those related to causality assessments, were extracted and compiled.

Results: Thirteen studies provided data on the prevalence of drug-related admissions. Seven studies focused on adverse drug reactions (prevalences 1.3-10%), and six studies used the broader concept of drug-related problems (prevalences 4.5-41%). In 10 out of 13 studies, causality between the drug and the specified problem was assessed. One study required a probable causal relationship; the remaining studies merely required a possible causal relationship. Five studies assessed the association between the problem assumed to be related to drug therapy and the admission, at one end requiring the former to be demonstrated as the underlying cause and, at the other, merely requiring a temporal relationship between drug intake and admission. Three out of eight studies involving multiple assessors for all/some cases reported the inter-rater agreement, ranging from none to almost perfect. Physicians were involved in the assessments in five studies, reporting prevalences of 3.2% to 4.5%, while studies without such medical input reported prevalences of 8.8% to 41%.

Conclusions: This review illustrates that methodological issues contribute to the diverse literature on drug-related admissions. We provide suggestions for harmonisation of research, including explicitly assessing the drug-problem-admission relationships from a medical perspective, focusing on problems where the drug treatment is the probable culprit.

KEYWORDS
adverse drug reaction, assessment, causality, drug-related admission, methodology, pharmacoepidemiology

1 | INTRODUCTION

Drug treatment has the potential to increase health but has also been reported to add a non-negligible burden for patients and healthcare; associated problems, including adverse drug reactions (ADRs), contribute to health problems and healthcare consumption that could possibly have been prevented.[1,2]

Clinically, problems suspected to be related to drug treatment are often difficult to distinguish from other medical conditions, including spontaneous emergence of diseases and worsening of present diseases. Indeed, ADRs can only be considered the culprit in healthcare after other potential causes have been ruled out. This often requires thorough clinical assessments, including an extensive medical history, physical examination, laboratory parameters, image diagnostics, etc.

From a scientific perspective, it may be intriguing that a systematic review from 2018, including 19 studies published up to 2016, shows that the prevalence of drug-related readmissions varied between 3% and 64% in individual publications.[1] Furthermore, from a clinical perspective, it may be surprising to learn that the most recent systematic review in PubMed, including 16 studies published in 2012-2017, reports that the average prevalence of drug-related admissions is still as high as 15%, with up to 41% of hospital admissions reported in individual publications,[2] despite efforts for rational use of medicines and improved prescribing practices over the last decades.

Recent systematic reviews have concluded that heterogeneity in research on preventable ADRs is a concern of substantial magnitude[3,4]; also, reliability is a known issue in ADR causality assessments.[5,6] We hypothesised that methodological aspects related to causality assessments could be contributing to the divergent figures on drug-related hospital admissions. By taking a deeper look at such methodological aspects in original studies contributing data to the most recent review, we aimed to understand the varying prevalences of drug-related admissions and provide suggestions for future harmonisation of research.

What is already known about this subject

- Numerous studies have investigated the prevalence of drug-related admissions.
- Systematic reviews investigating this topic reveal conspicuously varying results.

What this study adds

- Thirteen original studies that contributed data on the prevalence of drug-related admissions to a recent meta-analysis reported prevalences ranging between 1.3% and 41%. Among the 13, it appeared that only one study required a probable causal relationship to be demonstrated between the drug and the given problem. The remaining studies assessing causality used a cut-off point that allowed other causes to be just as likely. Only five studies described the relationship required between the problem assumed to be related to drug therapy and the hospital admission, for the admission to be considered drug-related. None differentiated between a causative and a contributory role of the problem at issue.
- Nonspecific designs contribute to the varying prevalence reported for drug-related admissions. For enhanced methodological rigour and harmonisation of future research, this paper provides explicit suggestions, including the suggestion to perform valid causality assessments.

2 | METHODS

This meta-epidemiological review, following suggested guidelines for this design,[7] included all original studies contributing data to the most recent meta-analysis on drug-related hospital admissions.[2] We recorded the impact factor of the scientific journals during the year when the individual articles were published, retrieved from InCites Journal Citation Reports.

Two authors (S.M.W. and J.L.) extracted data from the studies, and all three authors checked these. Data extraction included the initiating department, the setting, the patients, the study year/s and the reported prevalence of drug-related admissions, including whether drug-related problems, or ADRs only, were included in the numerator. We also recorded if the publication reported the number of drug-related admissions (numerator) and the number of total admissions (denominator), both required to calculate the prevalence of drug-related admissions.

Regarding causality, we recorded information about the association required between the drug and the given problem as well as between the problem assumed to be related to the drug therapy and the hospital admission, and about tools used for the assessments. We also recorded the number of assessors and their professional background and, if reported, the inter-rater agreement. In addition, we recorded whether the author/s had discussed the benefit-risk balance and the clinical context, and whether advice for practice based on the results and/or limitations of the study was provided in the abstract conclusion.

All authors discussed the assessments in an iterative process, providing suggestions for classifications, checking these and contributing additional information for further reconsideration and, potentially, reclassification. The assessors were specialists in clinical pharmacology knowledgeable in pharmacovigilance (S.M.W. and M.H.), and specialists in infectious diseases (M.H.) and internal medicine (J.L.). Disparities were resolved by discussion and consensus was reached. Finally, we made a summary of suggestions for harmonisation of future research to provide meaningful results for healthcare decision making.

A descriptive analysis of the data was performed. No ethics approval was required as no sensitive data were handled.

3 | RESULTS

A total of 16 studies[8–23] were included in the studied review.[2] In all, 88 individuals authored the publications written by four to nine authors, two authors appearing in more than one publication. For four publications, no impact factor was recorded for the specific journal.[10,14,15,17] For the remaining articles, the impact factor for the publishing journal ranged from 1.28[9] to 3.98.[16]

Thirteen studies provided data regarding the prevalence of drug-related admissions. The remaining three studies either investigated the proportion of emergency department visits, not admissions, that were drug-related[14,17] or investigated the association between potentially inappropriate drug use, according to indicators of prescribing quality, and hospitalisations[23] (Table 1). Seven of the 13 studies providing data on the prevalence of drug-related admissions came from European countries,[8,11,13,18,19,21,22] two came from the United States,[16,20] two from Asia,[12,15] and two from Saudi Arabia.[9,10] Three studies used register data,[10,16,21] while the remaining 10 used clinical cohorts. Two cohorts were restricted to oncology wards and cardiac transplant patients, respectively.[12,20]

Seven studies focused on ADRs, reporting prevalences of drug-related admissions between 1.3% and 10%,[8,11,16,18,19,21,22] while six studies focused on the broader concept of drug-related problems, reporting prevalences between 4.5% and 41%.[9,10,12,13,15,20] One study based its estimations on register data without assessing the specific cases[21]; the remaining 12 studies performed assessments (Table 2). In five studies reporting drug-related admission prevalences of 3.2-4.5%, a physician was involved in the assessments.[10,11,18,19,22] Four of these studies originated from French, German and Spanish pharmacovigilance centres.[11,18,19,22] In the remaining seven studies, reporting prevalences of 8.8-41%, primarily pharmacists performed the assessments.[8,9,12,13,15,16,20]

Out of 12 studies where cases were individually assessed, two did not report how the association between the drug and the given problem was determined and the required causality.[9,10] In the remaining 10 studies, such assessments were described; the Naranjo score was the most frequently used tool.[8,12,16,20] All but one study included problems with at least a possible causal relationship; the remaining study clearly stated that other causes had to be ruled out.[11]

Regarding the causality between the problem assumed to be related to the drug therapy and the hospital admission, no assessment was made in five studies[8–10,12,15] and the assessment was unclear in another two.[16,22] Among the remaining five studies, one was required to demonstrate that an ADR was the cause of the admission,[11] in two at least a possible relationship between an ADR and the admission diagnosis was required,[18,19] and the remaining two studies focused on drug-related problems and either used a cut-off point in a Likert scale[20] or required a demonstration of only a temporal relationship between the drug intake and the admission.[13] No studies differentiated between a causative and a contributory role of the specified problem.

Four out of eight studies involving multiple assessors, for all or some cases, provided some information about the inter-rater agreement.[8,15,16,20] Regarding the assessment of the relationship between the drug and the given problem, the agreement was described as "slight" (kappa 0.01-0.20) to "moderate" (kappa 0.41-0.60),[15] and two studies provided kappa values: 0.16[8] and 0.81.[16] Regarding the assessment of the relationship between the problem assumed to be related to drug therapy and the hospital admission, one study reported an inter-rater agreement of 0.9 using Cronbach's alpha.[20]

Overall, the complexity of drug treatment, where expected benefits have to be weighed against the risk of harms, was to some extent discussed in two studies.[16,19] The remaining 11 studies only discussed the risks of drug treatment. In the abstract conclusions, no studies mentioned the limitations of their study or presented cautions regarding the interpretation. Four studies provided no advice in the abstract conclusion,[12,16,18,19] five advocated improved prescribing practices,[8–11,15] and six suggested targeted interventions such as education[9,10,13,15] and/or preventive strategies such as multiprofessional teams/medication reviews.[9,13,20,22]

Based on the findings of this review, in Table 3 we make nine explicit suggestions to harmonise future research on the relationship between drug treatment and hospital admissions, and to reduce heterogeneity in meta-analyses.

DISCUSSION

Reviewing methodological aspects in original studies investigating drug-related admissions, we found that the manner in which causality assessments were performed may have contributed to the wide range in reported prevalences. Although the causality between the drug and the given problem was assessed in the majority of the studies, problems that could just as well originate from a disease or the worsening of a disease were included in all but one study. Furthermore, the causality between the problem assumed to be related to drug therapy and the hospital admission was only assessed in half of the studies, often in a nonspecific way and never differentiating between problems that contributed to the admission and problems that caused it. Prevalence figures at the lower end and a narrow range of results were reported when physicians and pharmacovigilance centres contributed to the assessments. Inter-rater agreement was reported in a minority of the studies, and when such information was provided, reliability often appeared to be an issue.

These methodological issues may contribute to the diverse prevalences of drug-related admissions reported in systematic reviews on the topic, some of which highlighted the heterogeneity as problematic in the abstract but still performed meta-analyses,[1,3,4,24] and some of which failed to include cautions regarding the encountered disparity.[2,25,26] Heterogeneity regarding study populations, as discussed elsewhere,[4] was also encountered among the studies in this review,

TABLE 1 Characteristics of the 16 publications included in a systematic review on drug-related hospital admissions[2]

Study	Initiator	Setting	Ward/patients	Study year/s	Data source	Patients (n)	DRP/ ADR	DRA (n (%)
Ahern et al (2014)[8]	Department of Pharmacy	Ireland, one hospital	ED	2010	Clinical cohort	856	ADR	75 (8.8% [7.0–10.9%])
Al-Arifi et al (2014)[9]	College of Pharmacy	Saudi Arabia, one hospital	ED	2011	Clinical cohort	300	DRP	52/251 (21%)
Alghamdy et al (2015)[10]	Department of Pharmacology	Saudi Arabia, one hospital	ED	2012	Register	5574	DRP	253 (4.5%)
Bénard-Laribière et al (2015)[11]	Pharmacovigilance centres	France, 61 hospitals	61 medical wards	2006–2007	Clinical cohort	2692	ADR	97 (3.6% [2.8–4.4%])
Chan et al (2014)[12]	Department of Pharmacy	Singapore, one hospital	Two oncology wards	2012	Clinical cohort	1275	DRP	158 (12.4%)
Gustafsson et al (2016)[13]	Division of Clinical Pharmacology	Sweden, two hospitals	Two medical wards, one orthopaedic ward/patients aged ≥65 with dementia or cognitive impairment	2012–2014	Clinical cohort	458	DRP	189 (41.3%)
Jatau et al (2015)[14]	Faculty of Health Sciences	Malaysia, one hospital	ED	2014–2015	Clinical cohort	434	DRP	NR (uses ED visits as denominator, admissions not reported)
Karuppannan et al (2013)[15]	Faculty of Pharmacy	Malaysia, one hospital	Two medical wards	2009–2010	Clinical cohort	1124	DRP	443 (39%) (n = 94 [8.4%] due to ADRs)
Marcum et al (2012)[16]	Department of medicine	US Veteran Affairs Medical Centers	152 departments/patients aged ≥65	2003–2006	Register	678	ADR	68 (10%)
Nickel et al (2013)[17]	ED	Switzerland, one hospital	ED/patients presenting with non-specific complaints	2007–2009	Clinical cohort	633	DRP	NR (uses ED visits as denominator, admissions not reported)
Pedros et al (2014)[19]	Pharmacovigilance centre	Spain, one hospital	Admissions through ER	2009–2010	Clinical cohort	4403	ADR	186 (4.2% (3.7–4.8%)
Pedros et al (2016)[18]	Pharmacovigilance centre	Spain, one hospital	Admissions through ER/patients aged ≥65	2008–2014	Clinical cohort	60 263	ADR	1976 (3.3% (3.1–3.4%)
Repp et al (2012)[20]	Cardiac transplant centre	US, one cardiac transplant centre	Cardiac transplant patients	2009–2010	Clinical cohort	48	DRP	19 (40%)
Ruiter et al (2012)[21]	Department of Epidemiology	The Netherlands, nationwide registry of hospital discharges	Patients aged ≥55	2000–2005	Register	2 127 133	ADR	26 852 (1.3%)
Schmiedl et al (2014)[22]	Pharmacovigilance centres	Germany, four hospital	Internal medicine departments	2000–2008	Clinical cohort	212 000	ADR	6887 (3.2%)
Sköldunger et al (2015)[23]	Ageing research centre	Sweden, two sites	Patients aged ≥60	2001–2004	Register	4108	NR	NR (reports about the association between potentially inappropriate drug use, according to indicators and hospitalisations)

Abbreviations: ADR, adverse drug reaction; DRA, drug-related admission; DRP, drug-related problem; ED, emergency department; ER, emergency room; NR, not reported; US, United States.

TABLE 2 Aspects related to assessments and reporting in 13 publications reporting data on prevalence of drug-related hospital admissions

		Relationship: drug–problem			Relationship: problem–admission			
Study	Assessors	Causality assessment	Required causality	Inter-rater agreement	Causality assessment	Required causality	Inter-rater agreement	Benefit–risk balance/clinical context discussed
Ahern et al (2014)[8]	Three pharmacists, one medical registrar Algorithm for decision, no consensus discussion	Yes	≥Possible (Naranjo)	Kappa 0.16	No	N/A	N/A	No
Al-Arifi et al (2014)[9]	One pharmacist	No	N/A	NA	No	N/A	N/A	No
Alghamdy et al (2015)[10]	Team consisting of physician, clinical pharmacologist, pharmacist	No	N/A	NR	No	N/A	N/A	No
Bénard-Laribière et al (2015)[11]	Independent adverse event evaluation committee: clinical pharmacologists, internists, and one general practitioner	Yes	Compatible with the initiation of drug treatment, and other causes ruled out	NR	Yes	If the ADR at hospital admission was not the cause of admission, the hospitalisation was not considered ADR-related	NR	No
Chan et al (2014)[12]	NR; all authors from pharmacy departments	Yes	≥Possible (Naranjo)	NR	No	N/A	N/A	No
Gustafsson et al (2016)[13]	Three pharmacists, independently and in consensus	Yes	≥Possible (WHO)	NR	Yes	Temporal relationship between drug intake and admission; drug treatment changes shortly before admission checked	NR	No
Karuppannan et al (2013)[15]	One pharmacist (10% of cases, randomly selected, were assessed by two pharmacist and one physician)	Yes	Study-specific criteria, wide	From "slight" (kappa 0.01–0.20) to "moderate" (0.41–0.60), kappa values not provided	No	N/A	N/A	No
Marcum et al (2012)[16]	Two pharmacists	Yes	≥Possible (Naranjo)	Kappa 0.81	Unclear	Naranjo, unclear how this instrument was used for this purpose	N/A	Yes
Pedros et al (2014)[19]	One clinical pharmacologist (MD)	Yes	≥Possible (SPhVS)	N/A	Yes	≥Possible relationship between ADR and admission diagnosis	N/A	No
Pedros et al (2016)[18]	One clinical pharmacologist (MD)	Yes	≥Possible (SPhVS)	N/A	Yes	≥Possible relationship between ADR and admission diagnosis	N/A	Yes

(Continues)

TABLE 2 (Continued)

Study	Assessors	Relationship: drug–problem			Relationship: problem–admission			
		Causality assessment	Required causality	Inter-rater agreement	Causality assessment	Required causality	Inter-rater agreement	Benefit–risk balance/clinical context discussed
Repp et al (2012)[20]	Three pharmacists	Yes	≥Possible (Naranjo)	NR	Yes	≥4 on the Likert scale (where 1 = no evidence that DRP was responsible for the admission, 6 = DRP definitely responsible for the admission)	Crohnbach's alpha = 0.9	No
Ruiter et al (2012)[21]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	No
Schmiedl et al (2014)[22]	Clinical pharmacologists (MD), pharmacists	Yes	≥Possible (Bégaud's algorithm)	NR	No	N/A	N/A	No

Abbreviations: ADR, adverse drug reaction; DRP, drug-related problem; MD, medical degree; N/A, not applicable; NR, not reported; SPhVS, Spanish Pharmacovigilance System; WHO, World Health Organization.

ranging from admissions through the emergency department to cardiac transplant patients. Furthermore, the original publications studied in this review focused on either ADRs or the more nonspecific concept of drug-related problems. Whereas the former term implies at least a possible relationship with patient harm,[27] the latter may include several other drug-related issues and does not require a problem to be manifested.[28] For instance, 37.5% of the DRPs identified in one study in this review were categorised as mild, defined as a laboratory abnormality or a symptom not requiring treatment.[9] Therefore, pooling ADRs and drug-related problems may contribute to heterogeneity and can be questioned, although it has been performed in some systematic reviews.[1,2]

3.1 | Causality: Drug-Problem

An important aspect of investigating the potentially harmful effects of drugs is that there needs to be a reasonable relationship between the drug and the problem. Therefore, it is encouraging that most of the studies included such an assessment. However, only one study required a probable causal relationship to be demonstrated between the drug and the given problem. The remaining studies in which this aspect was assessed had a lower cut-off as problems that had a possible causal relationship were included. Given the definition of such a relationship, the assumed problem related to drug therapy could just as well originate from the emergence or worsening of disease.[27]

In pharmacovigilance, where the aim is to detect signals of new and unknown ADRs, it is relevant to include and analyse individual case safety reports with a possible causal relationship between a drug and an event, the most frequent level of causality.[6] However, analyses of the prevalence of drug-related admissions do not aim to find unknown problems. Rather, they aim to quantify a healthcare problem for healthcare decision making. Therefore, it may be less relevant to include problems that may just as well have been caused by a disease. Indeed, one may speculate that the widespread use of a signal detection cut-off in descriptive prevalence studies may have contributed to an apprehension that we have frequently encountered, that harmful drug treatment is the major problem of healthcare.

3.2 | Causality: Problem-Hospital admission

To investigate drug-related admissions, the relationship between the problem assumed to be related to drug therapy and hospital admission needs to be determined. To elucidate, the problem may actually have caused the admission, that is, without this problem there would have been no admission. Alternatively, the problem may have contributed to the admission, that is, it was one factor among others that together resulted in the admission. For problems that merely coincide with the admission, there is no reason to identify the drug as the culprit and call the event a drug-related admission. We were surprised that seven out of 13 studies did not report that the relationship between the problem assumed to be related to drug therapy and the

TABLE 3 Methodological issues that contribute to the diverse prevalences of drug-related admissions reported in the scientific literature, including meta-analyses with unacceptable heterogeneity, and suggestions to harmonise future research to enable healthcare relevant estimates

No.	Issues identified	Suggestions for harmonisation
1	ADRs with a possible relationship with drug treatment are often included, ie events that could just as well be caused by a disease	When the aim is to quantify problems related to drug therapy in healthcare, ie not signal detection in pharmacovigilance, consider restricting the reported events to those with at least a probable causal relationship with drug treatment
2	The relationship between the problem assumed to be related to drug therapy and the hospital admission is often not assessed, and differentiation between a causative and a contributory role is not made	Assess and report the relationship between the problem assumed to be related to drug therapy and the hospital admission, and differentiate between problems that cause and problems that contribute to the hospitalisation
3	Reliability issues are often not reflected in the results, and when reported, the inter-rater agreement varies greatly	To illustrate the extent of subjectivity in the assessments, involve >1 assessor, describe their professional background and report inter-rater agreement
4	Low diversity in prevalences when physicians were involved in the assessments, and large diversity when they were not	To ascertain that the medical perspective is not overlooked, involve experienced physicians in drug-related causality assessments
5	Benefit–risk balance of drug treatment/ clinical context is rarely discussed	Discuss the benefit–risk balance of pharmacotherapy to remind readers that prescribing of drugs implies an inherent risk, and that the expected benefits, before problems occur, are usually expected to exceed the risks
6	Cautions in the interpretation of the results not visible in the abstract conclusions	Highlight limitations in the abstract conclusion
7	Advice for practice often provided in the abstract conclusion	If the aim of the study is to quantify a healthcare problem, the focus should be on preventable problems, ie, not presented problems that are part of the benefit–risk balance of the drug treatment at issue
8	The way "ADRs" and "drug-related problems" are treated as one issue	Analyse problems assumed to be related to pharmacotherapy, including ADRs, separately from drug-related problems. The latter issue, as opposed to the former, can by definition include problems that are not manifested in patients
9	Diversity of populations included in meta-analyses, from admissions through emergency departments without age restriction, to cardiac transplant patients	In meta-analyses, clearly define the patients to reduce clinical diversity

ADR, adverse drug reaction.

admission was formally assessed. Moreover, another three studies either merely required a temporal relationship to be demonstrated between the drug intake and the admission or used a Likert scale (presumably requiring a more than 50/50 probability that the problem was the cause of the admission, allowing close call events[29]) or used the Naranjo score, somehow extrapolated from the assessment of ADRs. These definitions can be considered fairly vague and they were applied from a pharmaceutical perspective, not a medical one. None of the studies differentiated between a causative and a contributory role of the problem assumed to be related to drug therapy, that is, none considered whether this problem was the sole factor or whether it was one of several factors that led to the admission.

3.3 | Inter-rater agreement

Inter-rater agreement was reported in some, but not all, studies using multiple assessors. When reported, the results were clearly divergent,

ranging from no agreement beyond chance to almost perfect agreement.[30] The use of established criteria cannot explain these findings; one study using the Naranjo scale reported low inter-rater agreement,[8] while another reported high inter-rater agreement.[16] However, another difference was more conspicuous between studies reporting high versus low inter-rater agreement. The two studies where pharmacists performed all assessments reported high inter-rater agreement,[16,20] whereas studies involving both pharmacists and physicians in the assessments reported low inter-rater agreement.[8,15] These findings could, at least to some extent, be explained by a recent reliability study reporting that the overall inter-rater agreement regarding drug-related admissions was moderate between three internists but weak between residents.[5] Indeed, assessments regarding the association between drug treatment and hospital admission may involve complexities that require extensive medical competence for reliable results; an ADR, for instance, is often a differential diagnosis as other reasons for the symptoms have to be ruled out. It can be speculated that these complexities would not be captured by assessors without a medical background, resulting in less divergent assessments. This reasoning is supported by a kappa of 0.45 which has been reported for the Naranjo Algorithm and the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) system, the latter relying more on assessor expertise.[6] Furthermore, the studies performed by pharmacovigilance centres showed fairly similar figures, suggesting that more reliable results can be obtained when experienced assessors with medical competence are used.

Interestingly, the reported prevalences of drug-related admissions were similar, below 5%, when at least one physician was involved in all assessments of specific cases. Without such medical input, the prevalence ranged up to 41%. In this context, it must be noted that studies both with and without physicians involved in the assessments reported percentages of both ADRs[8,10,16] and drug-related problems.[9,11–13,15,18–20,22] Hence, the broader definition of drug-related problems does not fully explain the divergent findings. Furthermore, the heterogeneity of the settings cannot account for the diversity of the results: the reported prevalences of drug-related admissions in studies including medical wards ranged between 3.2% and 41%.[11,13,15,22] Correspondingly, studies set in emergency departments studying hospital admissions reported prevalences between 3.3% and 21%.[8–10,18,19] It therefore seems reasonable to conclude that professional background may be reflected in the results. Nevertheless, the lack of consistency regarding current definitions, classifications and applications within the field of drug safety is problematic.[31]

3.4 | Benefit-risk balance

The benefit-risk balance was rarely discussed in the included studies. As the design by definition focuses on the risks and the benefits of treatment will not be captured, nuanced discussions may reduce the risk of unjustly discrediting pharmacotherapy, facilitating for the reader not to forget the beneficial effects that can also be expected for drugs often at issue in adverse events, including, for instance, anticoagulants and chemotherapy.[25]

An adverse event can be the consequence of a prudent benefit-risk evaluation and correct drug treatment, for instance septicaemia following lege artis anticancer treatment. Adverse events may also occur as a result of prescription errors (eg, an unsuitable drug or dose may have been chosen) or as a consequence of administration errors, miscalculated dilution or concomitant ingestion of chelating agents. Although all these events can be considered related to drug therapy, errors would probably be the primary interest from a healthcare perspective; these events could possibly be prevented. As discussed previously, the primary aim of quantifying drug-related admission is not the detection of new and unknown reactions, rather it is to describe a healthcare problem, and focusing on preventable errors could therefore be preferable from a healthcare decision-making perspective.

3.5 | Abstract presentation

The absence of caution in the abstract conclusion of the included studies regarding the interpretation of results is somewhat disappointing, although this has been previously reported.[32] In addition, we do not consider the advice that is often incorporated in abstract conclusions, and that draws attention to interventions, to be justified by the results. Interestingly, four out of six studies advocating targeted interventions in the abstract conclusion, including education and preventive strategies such as multiprofessional teams/medication reviews, reported prevalences of drug-related admissions between 21% and 41%.[9,13,15,20] As a comparison, the highest prevalence reported in studies without such advice in the abstract conclusion was 12%.[12] These findings raise the hypothesis that the magnitude of the quantified healthcare problem may be associated with the highlighting of advice for solutions, an aspect perhaps worth further consideration in future studies. Regardless of such speculations, the implications of abstract shortcomings are profound as the reading of scientific articles in a time-pressured medical practice may be limited to the abstract conclusion.

3.6 | Strengths and limitations

The most important strengths of this analysis are that it exposes methodological issues that contribute to the understanding of the varying results that are presented in systematic reviews on drug-related admissions and presents suggestions for harmonisation of future research. It may be argued that the review that formed the basis for the original articles studied here is not among the better ones. For instance, the inclusion of articles reporting the proportion of emergency department visits, not admissions, being drug-related may blur the results; not all visits result in a hospitalisation. Furthermore, the search in the origin systematic review was not performed and reported according to guidelines.[33] Therefore, it cannot be excluded that some studies were not captured. Nevertheless, the review

included publications from 2012 to 2017, with several of the pooled original studies having been published in well-renowned and established journals. The methodological problems encountered may consequently represent current research practice.

As our extraction of data, including the assessments, was complex, which is often the case in meta-epidemiological studies,[7] it may be regarded as a limitation that the extent of subjectivity could not be illustrated by kappa statistics. On the other hand, the iterative process applied can be expected to provide acceptably reliable results; available information was repeatedly and independently reconsidered by experienced assessors, ending up in consensus discussions and decisions. Another limitation is that we did not review the distinction between preventable and nonpreventable outcomes. This should be addressed in future studies.

4 | CONCLUSIONS AND IMPLICATIONS

This review shows that research on drug-related admissions is fraught with several methodological problems that may contribute to the wide range of reported prevalence. Causality seems to be a significant issue. For enhanced methodological rigour and harmonisation of future research, explicit suggestions are provided, such as to make medical assessments regarding the drug-problem and problem-admission relationships, and to focus on problems where the drug therapy is the probable culprit. Furthermore, the problem definitions and the benefit-risk balance of drug treatment deserve more attention, as does the content of the abstract conclusion. As systematic reviews play an essential role in evidence-based decision making, the issues identified in the present review should also be considered in evidence synthesis to reduce the risk of misinterpretations and hasty conclusions.

ACKNOWLEDGEMENTS

The study was funded by the Swedish Research Council (521-2013-2639), the Swedish state under the agreement between the Swedish government and the county councils (the ALF-agreement, ALFGBG-716941), and the NEPI foundation – Swedish Network for Pharmacoepidemiology. The funding sources did not influence the design, methods, data collection, analysis, preparation of the paper or decision to submit it for publication.

COMPETING OF INTEREST

There are no competing interests to declare.

CONTRIBUTORS

S.M.W. conceived the study. S.M.W., M.H. and J.L. designed the study and performed the assessments. S.M.W. performed the analyses and drafted the manuscript. M.H. and J.L. revised the manuscript for intellectual content.

DATA AVAILABILITY STATEMENT

Data sharing not applicable, no new data generated.

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How to cite this article: Wallerstedt SM, Hoffmann M, Lönnbro J. Methodological issues in research on drug-related admissions: A meta-epidemiological review with focus on causality assessments. *Br J Clin Pharmacol*. 2021;1-10. https://doi.org/10.1111/bcp.15012