PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Evidence synthesis based on non-randomised studies—a critical review of studies leading to conclusions on fall risk properties of loop diuretics/beta-blockers

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Abstract

Purpose To describe methodological and reporting issues in non-randomised comparative drug safety studies pooled in meta-analyses, with focus on confounding by indication.

Methods All studies included in statistically significant meta-analyses in a recent publication investigating fall risk properties of cardiovascular drugs were reviewed. Study characteristics were extracted and assessed.

Results Nine studies, including between 498 and 321,995 individuals, contributed data to the significant meta-analyses in which loop diuretics and beta-blockers were associated with falls, five published in 2015. Five individual studies reported a statistically significant association. In the five cohort studies, characteristics of exposed vs unexposed individuals were either not reported ($n = 3$) or differed substantially regarding morbidity ($n = 2$). Drug treatment was determined at baseline, and data on falls were collected for up to 2 years thereafter. Out of the four case-control studies, the cases and controls in only one study were matched for morbidity. Morbidity characteristics of fallers compared with non-fallers were either not reported ($n = 2$) or they differed ($n = 1$) or were reported according to the matched-for diseases ($n = 1$). Confounding by indication was explicitly discussed in two studies. None of the abstract conclusions considered causality issues or the possibility of confounding by indication.

Conclusions Confounding by indication is a major issue in non-randomised comparative drug safety studies, a problem which may be concealed in meta-analyses. To enhance such research, compared groups need to be balanced regarding relevant factors including morbidities and characteristics adequately reported. Confounding by indication needs to be explicitly discussed and highlighted in the abstract conclusion.

Keywords Drug safety · Cardiovascular drugs · Confounding by indication · Evidence-based medicine · Falls · Pharmacoepidemiology

Introduction

The basis for prescribing decisions is a medical assessment that the expected benefits of a drug exceed the risks for the specific patient, given their health condition. Therefore, the underlying evidence regarding benefits and harms, often summarised in systematic reviews and meta-analyses, is crucial in the process of prescribing. If the benefits are overestimated, patients will unjustifiably be put at risk. If, on the other hand, the risks are overstated, physicians may be guided to refrain from prescribing and the patients may not receive the benefits of treatment. Beneficial effects are generally well established through randomised controlled trials (RCTs), and meta-analyses of such studies are a standard procedure for evidence synthesis. Regarding safety aspects of drugs, not detected in RCTs, evidence often has to be based on non-RCTs using epidemiological methods, i.e. pharmacoepidemiological studies. When such studies are also pooled in meta-analyses, this may imply a considerably greater risk of bias, in particular because of selection bias and confounding by indication. Indeed, drug treatment is not random as physicians and, to a certain degree, patients make active and informed decisions.

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As clinical pharmacologists educating health care personnel and contributing as experts in pharmacotherapeutic contexts [1–3], we occasionally encounter the belief that fall risk properties of specific cardiovascular drugs are a major concern. Two previous systematic reviews published in 1999 [4] and 2009 [5] may have contributed to this belief, cited in 481 and 638 publications, respectively (Scopus, August 2019). Indeed, there are general recommendations against prescribing cardiovascular drugs because of fall risk properties, for example in sets of indicators of prescribing quality for older patients [6, 7]. A third, and the most recent, systematic review with meta-analyses evaluating cardiovascular drugs as risk factors for falls was published in 2018 [8]. It concluded that loop diuretics are associated with a 36% increased risk of falls and beta-blockers with a 12% decreased risk.

Confounding by indication has recently been reported to be the most prevalent methodological problem in pharmacoepidemiological research [9]. Meta-analyses that led to conclusions regarding associations between cardiovascular drugs and falls provide an opportunity to systematically take a deeper look at methodological and reporting issues, including confounding by indication, in current comparative drug safety research that contributes to prescribing recommendations. We performed the present study with the aim to elucidate these issues and to provide informed suggestions to enhance future research within the field.

Methods

In this study, we reviewed all publications contributing data to statistically significant meta-analyses in the most recent of the systematic reviews investigating cardiovascular drugs as a risk factor for falls, that is, those concerning loop diuretics and beta-blockers [8]. We extracted study characteristics and assessed methodological as well as reporting issues with a focus on aspects related to confounding by indication. We also recorded the impact factor of the scientific journals during the year in question, retrieved from the Journal Citation Index.

One author (S.M.W.) extracted data from the studies, and the other author (M.H.) independently checked these. Data extraction included the study design (retrieved from the meta-analysis [8]), the data sources used, characteristics of the individuals analysed, recording of drug exposure and collection of outcome data as well as information on the methodology used regarding matching and adjustments. Further, the results for loop diuretics and beta-blockers were extracted.

To shed light on issues related to confounding by indication, we recorded if morbidities of compared groups were presented according to the design. If presented, we assessed whether the compared groups differed regarding morbidity. We also determined whether confounding by indication was highlighted in the abstract and in the discussion section and

whether causality issues were considered. Finally, we recorded whether clinical advice was provided based on the results and whether there was a discussion on the benefit-risk balance of drug treatment.

The assessments were discussed by the authors in an iterative process where one author provided assessments and suggestions for classifications, and the other checked these and contributed with further information and suggested changes to the classifications. Disparities were resolved by discussion and consensus was reached.

A descriptive analysis of the data was performed. Based on the findings, we summarised suggestions to guide future research within the field.

Results

A total of nine studies were included in the review. In all, 60 individuals authored the publications which were each written by two to 17 authors. The impact factor of the journals in the year in which the studies were published ranged from 2.23 [10] to 6.35 [11].

In Table 1, characteristics of the studies are presented. The studies included 498 to 321,995 individuals, whose data were extracted either from registers ($n = 3$), from another study ($n = 4$) or were collected for the purpose of evaluating fall risk properties of drugs ($n = 2$). The patients came either from a general population sample ($n = 2$) or were nursing home residents (n = 2), inpatients ($n = 1$), older people with ability to walk ($n = 3$) or individuals who had experienced an ischaemic cerebrovascular event ($n = 1$). The mean age of the patients in the studies ranged between 70 and 84 years.

Five studies had a cohort design while the remaining four were case-control studies (Table 2). In the cohort studies, characteristics of exposed vs unexposed individuals were either not reported ($n = 3$) or differed substantially regarding morbidity ($n = 2$). In one of the latter studies, age also differed between the comparison groups [15]. In all case-control studies, the controls were matched for age and gender. Cases and controls were matched for morbidity in only one of the case-control studies. Morbidity characteristics between fallers and non-fallers were either not reported ($n = 2$) or differed ($n = 1$), or were reported according to the matched-for diseases ($n = 1$).

In the cohort studies, drug exposure was determined only at baseline, and falls were recorded during a follow-up period of 6 months to 2 years. All studies then applied a cross-sectional analysis. In three of the case-control studies, drug use was estimated from prescribed/dispensed drugs 30–60 days before the index date; in the fourth, the prescribed drugs in the medical records on the day of falling were used for the estimation.

Five studies reported a statistically significant association between loop diuretics and/or beta-blockers and falls (Table 1). In two of these, morbidities in the compared groups were

Table 1 Characteristics of reviewed studies

Author, year, country	Focus of study	Material	N (mean age, years)	Drug exposure	Outcome data collection	Results OR (95% CI) Beta-blockers	Results OR (95% CI) Loop diuretics	Clinical advice provided
Callaly et al. 2015 Ireland [12]	Falls and fractures among adults >18 years after first or new stroke or TIA	Clinical data from another study	124 fallers (71.7), 398 non-fallers (70.2)	Patient reported at baseline	Telephone questionnaire years 1 and 2	0.53 (0.32 to 0.89)	N/A	No
Chiu et al. 2015 Taiwan [10]	20 drug groups and falls during hospitalisation among patients ≥50 years without any recorded previous fall	Clinical data collected for this study	83 cases (71.6), 415 controls (71.6)	Cases: prescribed on day of falling Controls: unclear	Inpatient falls reported via an intranet web system	0.64 (0.14 to 0.83)	N/A	Should be mindfully prescribed and reviewed on a regular basis
Gribbin et al. 2010 UK [13]	Antihypertensives and falls among patients >60 years in general practice	Register data	9682 cases (77.5), 52,100 controls (76.4)	Main analysis: drugs prescribed <60 days before the index date	Read codes with description relating to falls	0.90 (0.85 to 0.96)	N/A	Clinicians to be alerted to the possibility of an increased risk of falls
Kuschel et al. 2015 Sweden [14]	20 drug groups and falls leading to hospitalisations, among all Swedish residents ≥65 yrs	Register data	64,399 cases, 257,596 controls (82.5*)	Drugs dispensed ≤30 days before the index date	Hospitalisation due to fall injury	Males: 0.77 (0.70 to 0.84), females: 0.89 (0.84 to 0.95)	Males: 1.32 (1.22 to 1.44), females: 1.14 (1.08 to 1.20)	Association with falls needs to be acknowledged for informed prescribing
Lim et al. 2009 USA [15]	Loop diuretics and falls among women ≥65 years with ability to walk unassisted and without bilateral hip replacement	Clinical data from another study	654 exposed individuals (79.4), 5827 unexposed individuals (76.6)	Patient reported at baseline	Postcards/telephone interviews at 4, 8 and 12 months	N/A	0.99 (0.71 to 1.39)	No
Lipsitz et al. 2015 USA [11]	Antihypertensives and falls among community-dwelling persons 70–97 years old with ability to walk across a room	Clinical data from another study	261 fallers (78.5), 331 non-fallers (78.3)	Patient reported at baseline	Postcards/telephone interview every month	1.09 (0.77 to 1.54)	N/A	Withholding antihypertensive drugs to prevent falls may not be justifiable
Marcum et al. 2015 USA [16]	Antihypertensives and falls among community-dwelling persons 70–79 years old who were well functioning, with ability to walk ¼ mile	Clinical data from another study	1677 exposed individuals (≥1 antihypertensive; 73.6), 1271 unexposed individuals (73.6)	Patient reported annually	Annual clinic/home visit/telephone check-up focusing on recurrent falls (≥2 per annum)	1.06 (0.82 to 1.36)	1.50 (1.11 to 2.03)	Clinicians should consider not prescribing loop diuretics because there may be an increased risk of recurrent falls
Mustard and Mayer 1997 Canada [17]	12 drug groups and association with falls among residents of nursing homes	Register data	1486 cases, 1486 controls (84.2*)	Drugs prescribed ≤30 days before index date	Hospitalisation due to fall injury	1.04 (0.64 to 1.63)	N/A	No

Table 1 (continued)

Author, year, country	Focus of study	Material	N (mean age, years)	Drug exposure	Outcome data collection	Results OR (95% CI)		Clinical advice provided
						Beta-blockers	Loop diuretics	
Reardon et al. 2012 USA [18]	Falls among nursing home residents > 18 yrs. old with registered Hb values, 57% identified as anaemic, 24% treated with anti-anaemia drugs	Cohort study with the aim to evaluate anti-anaemia drugs; antihypertensives was a covariable	177 exposed individuals (beta-blockers), 455 unexposed individuals (all 81.0)	Medical charts and pharmacy records at index date	Falls reported in the medical records	0.98 (0.56 to 1.73)	N/A	No

*Mean estimated by percentage figures provided in the publication

CI, confidence interval; *COPD*, chronic obstructive pulmonary disorder; *CV*, cardiovascular; *Hb*, haemoglobin; *N/A*, not applicable; *OR*, odds ratio; *TIA*, transient ischaemic attack; *UK*, United Kingdom; *USA*, United States of America

not considered in the analyses. Of the remaining studies, one study included the number of drugs as a covariate in the analyses, a factor that has been used as a proxy for morbidity [19], and two studies adjusted for a number of morbidities and medications used.

In four studies, the abstract conclusion highlighted the found fall risk properties of cardiovascular drugs. None of the conclusions in the abstracts considered causality issues or the possibility of confounding by indication. Confounding by indication was explicitly discussed in two out of nine studies and was vaguely described in another three. None of the concluding paragraphs of the discussions, however, mentioned confounding by indication.

The complexity of prescribing, taking into account the medical assessment of the benefit-risk balance for the specific patient according to the patient's current health condition, was discussed in one of nine studies [14]. Five studies provided clinical advice for prescribers, three of which highlighted that the identified increased fall risk should be an essential consideration in decision-making.

Based on the findings of this review, seven explicit suggestions were summarised to guide future comparative drug safety research using pharmacoepidemiological methodology (Box 1).

Box 1 Suggestions for enhanced comparative drug safety research using non-randomised observational data, based on findings in this review

1. Make efforts to balance the comparison groups regarding relevant factors including morbidities and concurrent drug treatment

2. Report characteristics of compared groups according to design

3. When a cohort design is stated, ensure that there is a reasonable time relationship between the drug intake and the event; otherwise, state that a cross-sectional design is used

4. Discuss confounding by indication explicitly, including the potential influence of this issue on the reported results

5. Relate safety aspect to expected benefits of the treatment, to ensure that the benefit-risk balance is reflected in the text

6. Refrain from providing explicit advice to prescribers based on single study results, such advice should be based on the compiled evidence

7. Highlight in the abstract conclusion, as well as in the last paragraph of the discussion, that non-randomised groups are compared and that confounding by indication cannot be excluded

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Discussion

In this review, we found that studies leading to the conclusion in a current meta-analysis of non-RCTs, that loop diuretics increase and beta-blockers decrease the risk of falls, had major methodological problems. For example, morbidity was not considered at all in two studies and only marginally in the rest. Further, characteristics of the compared groups were often inadequately described, severely limiting the potential for

interpretation of the findings. In addition, drug exposure was often not adequately handled; the possibility of confounding by indication was discussed in only a few studies; and causality considerations were not mentioned in any abstract.

The implications of our findings are serious as meta-analyses have an important role in evidence-based decision-making. Indeed, the term meta-analysis is connected to a high level of evidence. However, this is true only if based on RCTs without serious biases. Meta-analyses on non-RCTs, on the other hand, may be controversial. If aggravating issues in non-RCTs are not visible in the pooled results, there may be room for misinterpretations and hasty conclusions. In fact, the study that most influenced the results in the significant meta-analyses of loop diuretics and beta-blockers, because of its large study size, did not consider morbidity in the analyses other than to give, in numerical categories, the number of unique pharmacological subgroups (Anatomic Therapeutic Chemical classification (ATC), level 3 [20]), dispensed over a 120-day period from pharmacies [14]. One may speculate, based on medical common sense, that the results of the meta-analyses could be explained by prescribing practices, with beta-blockers being prescribed to those in better health and loop diuretics to those in worse. We have not reviewed the studies contributing to previous meta-analyses on associations between cardiovascular drugs and falls [4, 5], but they were all based on observational data with risks of confounding by indication.

An important aspect when investigating the effects of drugs is that there needs to be a reasonable time relationship between drug intake and reaction. Although studies with a cohort design are acknowledged to allow conclusions on causality, the potential to learn about fall risk properties of drugs may diminish when, as in this review, exposure is estimated at baseline and information on falls is collected for up to 2 years after baseline. Under these circumstances, it may be more informative to state that a cross-sectional design has been applied, thereby minimising the risk of misinterpreting causality.

Interestingly, three studies advised physicians to consider the fall risk increasing properties of drugs before prescribing. Given that all drugs have benefits and harms and that our review suggests that fall risk may be overstated because of methodological problems, it ought to be emphasised that one-sided attention to harms could contribute to withholding valuable treatment from patients. Still, all but one publication lacked a discussion on the benefit-risk balance of drug treatment. Although safety issues may require a less solid base of evidence, according to the ethical principle *not to harm others* and also the *better safe than sorry* principle, providing prescribing advice based on biased evidence implies risks. If a patient on antihypertensive drugs is orthostatic or their blood pressure is too low, it would probably not be controversial to suggest that these drugs should be withdrawn or the dose should be adjusted because the benefit-risk balance would not be expected to be positive for that specific patient. However, when a drug group is said to cause falls without putting

this within the context of clinical practice or science, readers may be confused and make hasty conclusions. Indeed, from a medical perspective, it is surprising that none of the studies provided information on blood pressure in the comparison groups.

In a time-pressured medical practice, reading of scientific articles may be limited to reading the abstract conclusion and the summarising paragraph at the end of the discussion. Therefore, our finding that these sections of the studies did not include important aspects for interpretation is somewhat disappointing. Although the limitations may be adequately discussed in some cases, the average reader may miss them. Similarly, readers of systematic reviews may miss cautions raised in the discussion if these are not also highlighted in the abstract conclusion. Indeed, the authors of the meta-analysis appraised in this review acknowledged in the discussion, but not in the conclusion of the abstract, that residual confounding by indication could not be ruled out as this was only partly addressed in the included studies [8]. To further facilitate interpretation, one may also consider requiring information on the type of studies pooled in the title, labelling the study as a *non-RCT meta-analysis* as opposed to an *RCT meta-analysis*.

To enhance the standards of comparative drug safety research, we provide suggestions regarding methodological and reporting issues (Box 1). Propensity score matching represents one technique to reduce the risk of confounding. Although one study used propensity scores as a covariate in a sensitivity analysis [15], none of the reviewed studies used this matching technique. According to findings of drug effectiveness studies [21], propensity score matching seems to have undergone limited divergence within the research on drug safety. Further, sensitivity analyses may be a valuable tool in pharmacoepidemiological research. One of the reviewed studies performed a sensitivity analysis in which antidepressants were used as a positive control [13]. As far as we are aware, however, the studies contributing to meta-analyses suggesting fall risk properties of antidepressants have not been reviewed. Therefore, it cannot be excluded that biases may have contributed to the significant findings on that drug group as well. Indeed, the association between antidepressants and fractures, a severe result of a fall, has recently been questioned [22].

Strengths and limitations

The most important strength of this review is that it highlights pertinent methodological and reporting problems within comparative drug safety research based on non-randomised observational data, providing illustrative examples that may contribute to misleading results in meta-analyses [23, 24]. In addition, explicit suggestions for enhanced performance of such research are provided. Another strength of the present study is that it starts off from a recent review of fall risk properties of cardiovascular drugs, thereby reflecting current practice. Furthermore, the assessments were performed by two clinical

Table 2 Methodological and reporting issues related to confounding by indication in studies contributing data to meta-analyses in a recent publication concluding that loop diuretics and beta-blockers are associated with falls

Author year country	Methods			Morbidity of compared groups reported**/differed	Discussion		Abstract conclusion	
	Design*	Matching	Adjustments		CBI discussed/ explicitly mentioned	CBI mentioned in conclusion/last paragraph/key points	Fall risk properties of CV drugs reported	Precautions regarding causality/CBI highlighted
Callaly et al. 2015 Ireland [21]	Cohort, with a cross-sectional analysis over 2 years	N/A	Age, gender	No	No/no	No	No	No
Chiu et al. 2015 Taiwan [10]	Case-control	Age, sex	Age, sex, length of hospital stay before the day of the index fall	Yes/yes	No/no	No	Yes	No
Gribbin et al. 2010 UK [17]	Case-control	Age, gender, practice	CHD, Charlson comorbidity index, other antihypertensives	No	Yes/no	No	Yes	No
Kuschel et al. 2015 Sweden [15]	Case-control	Gender, birth date, place of residence	Number of drugs	No	Yes/yes	No	Yes	No
Lim et al. 2009 USA [12]	Cohort, with a cross-sectional analysis over 1 year	N/A	Age, time-dependent weight, functional status, daily calcium intake, physical activity, self-reported health status, CHF, COPD, type 2 diabetes mellitus, smoking status and ≥2 falls in the year before baseline	Yes/yes	Yes/no	No	No	No
Lipsitz et al. 2015 USA [11]	Cohort, with a cross-sectional analysis over 1 year	N/A	Baseline BP, comorbidity count, education, race, BMI, psychotropic medication use and time spent in outdoor activities	No	Yes/no	No	No	No
Marcum et al. 2015 USA [22]	Cohort, with a cross-sectional analysis repeated annually over 5 years	N/A	Forced into the model: site, heart failure, BPH, cognitive impairment, depressive symptoms, self-reported hypertension, drugs with increased risk of falls; forward selection: education, age, marital status, alcohol use, cerebrovascular disease, diabetes, pulmonary disease, arthritis, urinary problems, vision problems, total number of prescription medications, syncope	Yes/yes	No/no	No	Yes	No
Mustard and Mayer 1997 Canada [23]	Case-control	Age, sex, level of dependency, duration of residence, up to five chronic disorders	12 medication exposure measures	Yes/not assessable as only matched-for morbidities were reported	Yes/yes	No	No	No
Reardon et al. 2012 USA [24]	Cohort, with a cross-sectional analysis over 6–18 months	N/A	Age, sex, race, mobility, Hb, renal function, diseases and conditions (n = 16); current medication (diuretics, psychoactive drugs, beta-blockers, anaemia treatment)	No: morbidities reported according to exposure to anaemia drugs	No/no	No	No	No

*According to the meta-analysis [8]

**According to design and regarding cardiovascular drugs. Cohort studies: exposed vs unexposed; case-control studies: fallers vs non-fallers

BMI, body mass index; *BP*, blood pressure; *BPH*, benign prostatic hyperplasia; *CBI*, confounding by indication; *CHD*, coronary heart disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disorder; *CV*, cardiovascular; *Hb*, haemoglobin; *N/A*, not applicable; *UK*, United Kingdom; *USA*, United States of America; *TIA*, transient ischaemic attack

pharmacologists knowledgeable in pharmacoepidemiology and with experience in evidence-based decision-making, both at the patient and at the societal level.

In the review, we chose to focus on cardiovascular drugs with a statistically significant association with falls, according to the meta-analysis. This may be regarded as a limitation affecting the generalisability of the results. Indeed, it cannot be excluded that the reviewed studies represent the better research in the field as they were all published in established journals with acceptable impact factors. Further, they were assessed to be of high or intermediate quality in the original systematic review [8]. Nevertheless, this approach was sufficient to highlight common pitfalls in comparative drug safety research.

Conclusion

This review illustrates that methodological and reporting issues are prevalent in comparative drug safety studies using non-randomised observational data, especially regarding confounding by indication. Although seemingly clear and informative, meta-analyses of non-RCTs may bear a risk to conceal such shortcomings. Increased awareness of these issues among researchers is crucial to enhance research within the field and caution recommended when results are pooled in meta-analyses. Authors of pharmacoepidemiological studies are encouraged to explicitly discuss and highlight in the abstract methodological limitations such as confounding by indication when non-randomised data are used to investigate outcomes of drug treatment.

Compliance with ethical standards

Ethical approval No ethics approval was required as no sensitive data were handled.

Competing interests The authors declare that they have no competing interests.

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