PHARMACOEPIDEMIOLOGY

Evaluating beneficial drug effects in a non-interventional setting: a review of effectiveness studies based on Swedish Prescribed Drug Register data

Correspondence Susanna Wallerstedt, Department of Pharmacology, Sahlgrenska Academy, University of Gothenburg, Box 431, SE-405 30 Gothenburg, Sweden. Tel.: +46 3 1786 3410; Fax: +46 3 1786 3164; E-mail: susanna.wallerstedt@pharm.gu.se

Susanna M. Wallerstedt[1,2] and Mikael Hoffmann[3]

[1]Department of Pharmacology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [2]Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden, and [3]The NEPI foundation – Swedish Network for Pharmacoepidemiology, Linköping University, Linköping, Sweden

AIMS

To describe and assess current effectiveness studies published up to 2014 using Swedish Prescribed Drug Register (SPDR) data.

METHODS

Study characteristics were extracted. Each study was assessed concerning the clinical relevance of the research question, the risk of bias according to a structured checklist, and as to whether its findings contributed to new knowledge. The biases encountered and ways of handling these were retrieved.

RESULTS

A total of 24 effectiveness studies were included in the review, the majority on cardiovascular or psychiatric disease ($n = 17$; 71%). The articles linked data from four (interquartile range: three to four) registers, and were published in 21 different journals with an impact factor ranging from 1.58 to 51.66. All articles had a clinically relevant research question. According to the systematic quality assessments, the overall risk of bias was low in one (4%), moderate in eight (33%) and high in 15 (62%) studies. Overall, two (8%) studies were assessed as contributing to new knowledge. Frequently occurring problems were selection bias making the comparison groups incomparable, treatment bias with suboptimal handling of drug exposure and an intention-to-treat approach, and assessment bias including immortal time bias. Good examples of how to handle bias problems included propensity score matching and sensitivity analyses.

CONCLUSION

Although this review illustrates that effectiveness studies based on dispensed drug register data can contribute to new evidence of intended effects of drug treatment in clinical practice, the expectations of such data to provide valuable information need to be tempered due to methodological issues.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- For rational use of medicines, a positive benefit/risk balance and an acceptable cost/benefit ratio is essential. A basic prerequisite for assessing this balance and ratio is relevant and adequate evidence on drug effectiveness, that is, the intended beneficial effects of a drug in clinical practice.
- Register research is expected to provide evidence on drug effectiveness, but the evidence achieved, when data collected in a non-interventional setting are used, has not been systematically assessed.
- During the first decade after the establishment of the Swedish Prescribed Drug Register (SPDR), 24 out of 338 publications based on SPDR data concerned drug effectiveness, constituting a representative sample of current studies on the topic.

WHAT THIS STUDY ADDS

- In this review, two out of 24 effectiveness studies based on data from SPDR contributed to new knowledge on beneficial drug effects in clinical practice, and only one study had a low risk of bias.
- Researchers performing and reviewing drug effectiveness studies, as well as decision makers interpreting the results, need to pay particular attention to selection, treatment and assessment biases.
- Propensity score matching, within-individual analyses and sensitivity analyses concerning population studied, drug exposure and outcomes represent ways to handle methodological challenges associated with drug effectiveness studies.

Table of Links

LIGANDS
Acetylsalicylic acid
Clopidogrel
Metformin
Warfarin

This Table lists key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

Introduction

A basic prerequisite for rational use of medicines and wise decisions on drug treatment, at both societal and patient levels, is access to relevant and adequate evidence. We need to know that every drug has a positive benefit/risk balance, as assessed initially upon approval by the drug authorities and thereafter by physicians when prescribing a drug to a specific patient. As health care resources are limited, we also need to know that the costs for a drug are reasonable given its effects, as for example illustrated by the cost/benefit ratio assessed by health technology assessment (HTA) authorities. In order to make these assessments, decision makers, including physicians, want to know about the size of the intended beneficial effects of a drug. Such information can be obtained from randomized controlled trials, reflecting the *efficacy* of a drug. However, as patients in health care differ in many respects from study participants, evidence of the intended effects of a drug in clinical practice, that is, the *effectiveness*, is desirable. In this context, increased attention has been drawn to register data, representing the non-interventional setting [2].

Prevailing expectations are that register data will provide information on drug effectiveness needed for decision making. In fact, for new drugs targeting unmet medical needs, these expectations may have contributed to the introduction of accelerated approval processes to facilitate rapid market entrance [3]. Such processes imply that less extensive evidence on drug effects is required before approval, and leave much of the generation of evidence to the post-approval stage. Indeed, the number of new drugs approved on the basis of single-arm studies, i.e. prospective case series without a concurrent control group, is increasing [4].

Great efforts are invested in collection of register data; however, as far as we are aware, the evidence achieved, concerning drug effects, when such data are used has not been systematically evaluated. As evidence regarding intended beneficial effects needs to be stronger than evidence on safety concerns, according to the *benefit of doubt* and the *better safe than sorry* principles, effectiveness studies are of particular interest. Indeed, spontaneously reported adverse drug reactions may suffice to reinforce the re-evaluation of drug safety issues [5], whereas beneficial effects need to be more convincingly proved. Therefore, we need to know to what extent register data can contribute to new evidence on intended beneficial effects of drug treatment, using today's methodologies.

Swedish national health registers are acknowledged worldwide as they are generally of good quality and cover the entire Swedish population. Furthermore, they hold much information, including, for example, health data and civic information, which can be linked via citizens' unique personal identity number [6]. They can also be linked to other data sources, including clinical data in electronic medical records transferred to a data warehouse or a quality register. The Swedish Prescribed Drug Register (SPDR) was expanded on 1 July 2005 to include the identity of the patient [7]. As all

pharmacies in Sweden are required by law to submit data on dispensed prescription drugs, the SPDR contains more than one decade of patient-level data on all dispensed prescription drugs in the country and may constitute a valuable data source for drug effectiveness studies.

In a recent systematic review describing the scientific output of the SPDR during the first 10 years after its establishment, all identified publications were categorized according to study type [8]. The basis for that review was a broad literature search strategy, using the terms 'drug', 'register' and 'Swedish' in different combinations, with alternative wordings. Further, additional publications were identified by personal knowledge, reference lists, contact with active authors and a citation search of the Web of Science database (for search details, see Wallerstedt *et al.* [8]). As Sweden has a long tradition in epidemiology [9], publications in the described review, categorized as effectiveness studies, may serve as a representative sample of effectiveness studies today. Indeed, the identified studies were published in a wide range of journals, including top-ranked journals on general medicine, and medium- and low-ranked journals with a more specific focus. Consequently, the articles can be expected to reflect both pitfalls and good examples. The aim of this study was to describe and assess effectiveness studies published up to 2014 and using data from the SPDR, with a focus on lessons for the future when it comes to design, methods and reporting.

Methods

In the present review, we have included 24 articles characterized as effectiveness studies in a previous systematic review (Figure 1) [8].
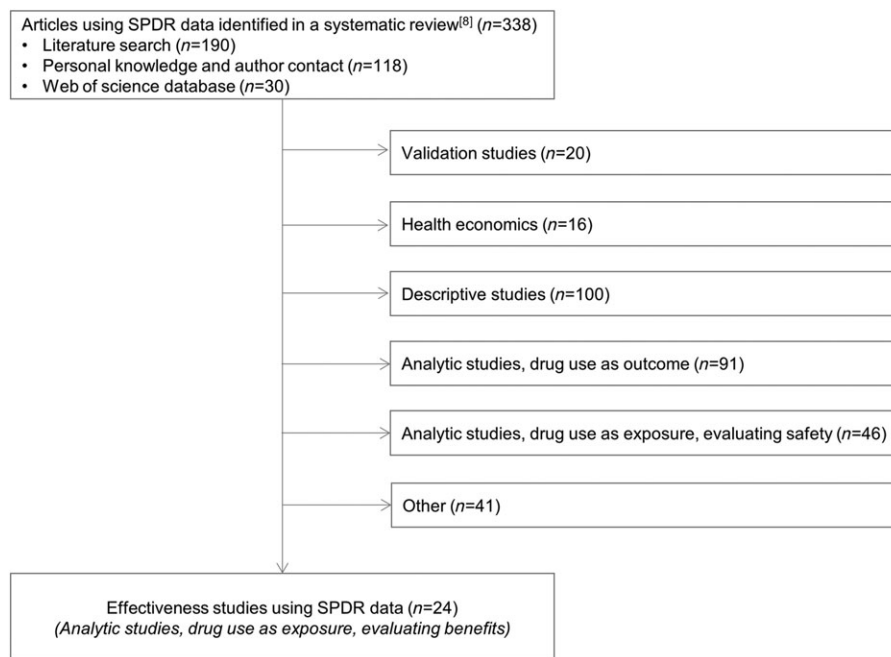
Data extraction

One author (S.M.W.) extracted data from the studies, and the other author (M.H.) checked these. Data extraction included the design of the study as well as the studied therapeutic area including drug(s) and outcome(s). We also recorded information regarding registers used, authors, open access publishing and impact factor of the scientific journals during the year in question, retrieved from Journal Citation Index.

Study assessments

All assessments were performed independently by both authors, after which any disparities were resolved by discussion, and consensus reached. To coordinate the assessments, we first assessed and discussed a random sample of four studies. After consensus was reached, we independently assessed and then discussed the remaining studies.

The initial assessment concerned clinical relevance. Here, we simply judged whether the research question was of interest to health care and the decision makers, based on our expertise in clinical pharmacology [10–12].

As a next step, we assessed the study quality according to a checklist on observation studies from the Swedish Council on Health Technology Assessment [13], including aspects of six biases (selection, treatment, assessment, exclusion, reporting, and conflicts of interest), weighed together in an overall assessment of study quality as having a low, moderate or high risk of bias. The biases encountered and ways of handling them were noted.

Finally, we assessed each study as to whether its results contributed to new knowledge or not. For this assessment, we used our experience as clinical pharmacologists as well as the study's introductory text reflecting the state of

Figure 1
Flowchart of studies based on Swedish Prescribed Drug Register (SPDR) data and included in the present review

knowledge. We also considered the credibility of the results, given the methodology used.

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

Statistics

Descriptive analyses were performed using SPSS, version 20.0 (IBM SPSS Statistics for Windows, Armonk, NY). Kappa statistics were used to assess inter-rater agreement on the study assessments. Values are presented as numbers (percentages) or medians (interquartile ranges).

Results

Characteristics of the 24 reviewed effectiveness studies are presented in Table 1. The majority were designed as cohort studies (n = 21; 88%). The therapeutic area most often focused upon was cardiovascular disease (n = 11; 46%), predominantly concerning antiplatelet agents (n = 6) and/or warfarin (n = 3). The six (25%) studies within psychiatry concerned mainly antipsychotics (n = 3) and medications for attention deficit hyperactivity disorder (ADHD) (n = 3). The five studies (21%) within the field of cancer concerned acetylsalicylic acid (n = 3) and tyrosine kinase inhibitors (n = 2).

The articles were authored by a median of five (four to seven) persons. In all, 103 authors were involved in the studies, 39 (38%) of whom acted as main authors, that is, appeared as first or last names. The articles were published in 21 different journals with an impact factor ranging from 1.58 to 51.66, median 4.78 (2.74–14.40). Ten studies (42%) were published under Open Access conditions.

Each publication used data from two registers or more, linked by patients' personal identity number. The studies linked data from a median of four (three to four) registers. In addition to SPDR data, the studies most often used health data from either the National Board of Health and Welfare (Patient Register: n = 19; Cause of Death Register: n = 16) or quality registers (n = 5) such as the National Diabetes Register, and civic information from Statistics Sweden (n = 8).

Regarding the study assessments, the inter-rater agreement was good (kappa = 0.79). We assessed all articles to have had a clinically relevant research question. According to the systematic quality assessments, the risk of bias was low in one (4%), moderate in eight (33%) and high in 15 (62%) articles (Table 1). Moderate and high risk of bias related to selection (n = 19; 79%), treatment (n = 23; 96%), assessment (n = 19; 79%), exclusion (n = 5; 21%), reporting (n = 24; 100%) and conflicts of interest (n = 8; 33%).

Issues related to different biases identified in the publications – in other words, problems and ways to handle them – are presented in Table 2, with corresponding reference to the publications illustrating these to various extents. An evident problem concerned the comparison groups. In ten (42%) studies, characteristics of these groups were not reported, and in nine (38%) studies, the groups differed importantly. Further, we identified two frequent problems related to the assessments of drug exposure. Firstly, in eleven (46%) studies, the exposure was only assessed at baseline mimicking intention-to-treat analyses

in randomized controlled trials. Secondly, in six (25%) studies, the exposure was suboptimally estimated given the dispensed drug data, for example by defining exposure as the time between drug dispensings rather than as a specified time after dispensings.

A good example of how to handle selection bias was the use of propensity score matching. This performance was particularly successful in a publication that was based on extensive data from a quality register and allowed control patients to differ by ≤0.01 [14]. Another good example, for handling selection, treatment, assessment, and exclusion biases, was the use of sensitivity analyses. Twelve (50%) studies performed at least one such analysis [14–25]. The analyses concerned population studied, drug exposure, outcomes, as well as missing data. In six (25%) studies, sensitivity analyses were performed within more than one of these domains. No studies provided a predefined protocol to minimize the reporting bias. Thirteen (54%) studies were entirely publicly funded, avoiding conflicts of interest bias.

Among nine studies with low or moderate risk of bias, two were assessed to contribute to new evidence for intended beneficial effects of drugs (Table 1) [14, 23]. The others either confirmed prevailing evidence (n = 4) [26–29] or had methodological problems, hampering the credibility of the results (n = 3) [15, 16, 19]. The six studies explicitly funded by the pharmaceutical industry focused on therapeutic areas with new treatment alternatives, and had either a high risk of bias (n = 4) or supported prevailing evidence (n = 2).

Discussion

In this review, we illustrate that effectiveness studies, using register data on dispensed prescription drugs, focus on relevant research questions. However, few of the published studies passed the overall assessment of evidence, as only two out of 24 publications contributed to new knowledge on intended beneficial effects of drug treatment in clinical practice, and only one publication had a low risk of bias. Moreover, our review illustrates that drug effectiveness studies can be funded by public means and published in high-impact journals. Therefore, our results are encouraging, on the one hand, as they illustrate the scientific endeavour for methodological advancements within a challenging field, as well as the willingness of public funders to support this kind of research and of high-impact journals to publish the results. On the other hand, our results indicate that the expectations need to be tempered concerning the ability of research based on data from a non-interventional setting to give decision makers, including physicians, relevant information for benefit/risk and cost/benefit assessments, given the status of drug effectiveness studies today. The same applies to the expectation that post-approval register-based studies will provide missing evidence for drugs approved by single-arm studies.

Interestingly, this review probably reflects the better subset of evaluations of drug effectiveness from register data. Indeed, for every published study, there may be numerous negative studies that are not publicly available. Further,

Table 1

Characteristics of studies included in the review, as well as resulting assessments

Author	Therapeutic area	Design	Drug/drug group	Outcome studied	Risk of bias						COI	Overall risk	Contributes to new knowledge
					Selection	Treatment	Assessment	Exclusion	Reporting				
Ambring et al. [42]	Cancer	Cohort	Tyrosine kinase inhibitors	Time to death, duration of treatment	High	High	Low	Low	Moderate	High	High	No
Björck et al. [43]	CVD	Case/control	Warfarin	Stroke	High	High	Low	Low	Moderate	Moderate	High	No
Bodén et al. [26]	Psychiatry	Cohort	Antipsychotics	Rehospitalization, time to first relapse	Moderate	High	Moderate	Low	Moderate	Moderate	Moderate	No
Chang et al. [15]	Psychiatry	Cohort	ADHD medication	Serious transport accident	Low	High	Moderate	Low	Moderate	Low	Moderate	No
Chen et al. [16]	Psychiatry	Cohort	ADHD medication	Suicide-related events	Low	High	Moderate	Low	Moderate	Low	Moderate	No
Ekström et al. [34]	CVD	Cohort	Metformin	CVD, mortality, acidosis/serious infection	High	High	Moderate	Low	Moderate	Low	High	No
Ekström, Hermansson et al. [17]	CVD	Cohort	ACEI, antiplatelets, betablockers, statins	Mortality	High	High	High	High	Moderate	Low	High	No
Ekström, Cederholm et al. [18]	CVD	Cohort	ASA	CVD, CHD, stroke, mortality, bleedings	High	High	Moderate	High	Moderate	Low	High	No
Eliasson et al. [35]	CVD	Cohort	Lipid-lowering drugs	Lipid levels	High	High	Low	High	Moderate	Moderate	High	No
Fazel et al. [19]	Psychiatry	Cohort	Antipsychotics and mood stabilizers	Violent crime conviction	Low	High	Moderate	Low	Moderate	Low	Moderate	No
Forslund et al. [44]	CVD	Cohort	ASA, warfarin	Ischaemic stroke, bleeding, death	High	High	Moderate	Low	Moderate	Low	High	No
Friberg et al. [27]	CVD	Cohort	Warfarin	Net benefit (avoided stroke minus excess intracranial bleeding)	Moderate	High	Low	Low	Moderate	Moderate	Moderate	No
Holmes et al. [20]	Cancer	Case/control	ASA	Breast cancer death	Moderate	High	High	Low	Moderate	Low	High	No
Jonasson et al. [28]	Gastrointestinal disease	Case/control	PPI adherence in NSAID users	Peptic ulcer, bleeding	Moderate	Moderate	Moderate	Low	Moderate	High	Moderate	No
Jonsson et al. [21]	Cancer	Cohort	ASA	TNM characteristics	High	Moderate	High	Moderate	Moderate	Low	High	No

(continues)

Table 1

(Continued)

Author	Therapeutic area	Design	Drug/drug group	Outcome studied	Risk of bias						Overall risk	Contributes to new knowledge
					Selection	Treatment	Assessment	Exclusion	Reporting	COI		
Landfeldt et al. [22]	Osteoporosis	Cohort	Bone-active drugs	Osteoporotic fractures related to persistence	High	Moderate	Moderate	Low	Moderate	High	High	No
Lichtenstein et al. [23]	Psychiatry	Cohort	ADHD medication	Crime conviction	Low	High	Moderate	Low	Moderate	Low	Moderate	Yes
Ljung et al. [45]	Cancer	Cohort	Antiplatelets	Lymph node metastasis	High	High	High	Low	Moderate	Low	High	No
Lund et al. [14]	CVD	Cohort	Betablockers	All-cause mortality, HF hospitalisation	Low	Low	Low	Low	Moderate	Low	Low	Yes
Ringback Weitoft et al. [46]	Psychiatry	Cohort and case/control	Antipsychotics	Death, suicide, suicide attempt, rehospitalization, prescription refill	High	High	Moderate	Low	Moderate	Low	High	No
Själander et al. [24]	CVD	Cohort	ASA	Ischaemic stroke, thromboembolic events, intracranial haemorrhage, major bleeding	High	High	Moderate	Low	Moderate	Low	High	No
Wahlgren et al. [47]	Cancer	Cohort	Tyrosine kinase inhibitors	Overall survival	High	High	High	Low	Moderate	High	High	No
Wang et al. [25]	CVD	Cohort	Clopidogrel and PPI	Recurrent AMI, stroke, angina, all-cause mortality	High	Moderate	Moderate	Moderate	Moderate	Low	High	No
Welin et al. [29]	CVD	Cohort	ASA	Mortality, bleeding	High	Moderate	Moderate	Low	Moderate	Low	Moderate	No

ACEI, angiotensin converting enzyme inhibitor; ADHD, attention deficit hyperactivity disorder; AMI, acute myocardial infarction; ASA, acetylsalicylic acid; COI, conflict of interest; CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; TNM, tumour extent, nodal involvement, metastatic status.

Table 2

Issues related to different biases identified in the publications, either a problem (P) or a way to handle a problem (H). Values are presented as number of articles (percent) in which the issue was encountered

Bias	Issue	Type	n (%)	Reference number
Selection	Characteristics of comparison groups not reported	P	10 (42)	[20–22, 25, 26, 28, 29, 35, 43, 47]
	Important differences between comparison groups	P	9 (38)	[17, 18, 24, 27, 34, 42, 44–46]
	Within-individual comparison	H	4 (17)	[15, 16, 19, 23]
	Propensity score matching	H	2 (8)	[14, 24]
	Sensitivity analysis concerning studied population	H	8 (35)	[14–16, 18–20, 23, 24]
Treatment	'Intention to treat' analysis	P	11 (46)	[18, 24–27, 34, 35, 43, 44, 46, 47]
	Estimation of drug exposure suboptimally handled	P	6 (25)	[15, 16, 19, 23, 29, 47]
	Exposure not satisfactorily covered by SPDR data	P	1 (4)	[47]
	Sensitivity analysis concerning treatment exposure	H	8 (33)	[14–16, 19, 21–23, 25]
Assessment	Order of causality, confounding by indication	P	9 (38)	[17, 19–21, 23–25, 44, 46]
	Immortal time bias	P	4 (17)	[22, 25, 27, 47]
	Design does not answer the research question	P	3 (13)	[21, 26, 45]
	Sensitivity analysis concerning outcome	H	5 (21)	[15, 16, 19, 20, 23]
Exclusion	Missing register data	P	3 (13)	[18, 34, 35]
	Sensitivity analysis, imputation	H	1 (4)	[17]
Reporting	Unclear whether the protocol was defined beforehand	P	24 (100)	[14–29, 34, 35, 42–47]
Conflict of interest	Funding from the industry	P	6 (25)	[22, 26, 28, 35, 42, 47]
	Author reported involvement in industry activities	P	7 (29)	[14, 22, 27, 28, 34, 43, 47]
	Only public funding reported	H	13 (54)	[14–17, 19, 21, 23–25, 43–46]

effectiveness evaluations performed under circumstances other than scientific publishing, for example by the pharmaceutical industry in applications for reimbursement, do not undergo formal peer review. Although not evaluated in this review, it may be speculated that use of register data in that context may be highly biased as it lies in the interests of the applicant to show large drug effect size.

As, owing to ethical and regulatory issues [30–32], randomization has not yet been implemented in drug effectiveness studies, our review highlights the importance of taking advantage of methodology developed to minimize differences between comparison groups. Indeed, in only one study in this review, the control group did not differ considerably from the intervention group. In all other studies making between-groups comparisons, the groups differed in important aspects, or information on characteristics of comparison groups was missing and important differences could be anticipated.

Propensity score matching represents one technique to reduce the risk of confounding. Our review illustrates that taking advantage of data from quality registers, focusing on certain conditions or procedures [33], in a narrow matching procedure, may be a successful approach. Indeed, administrative health databases including dispensed prescription drugs and diagnoses may not be sufficient to retrieve essential clinical patient data. On the other hand, quality registers may suffer from incomplete data, which is illustrated by the fact that, in this review, some studies exclude a large proportion of the patients for this reason [18, 34, 35]. Indeed, to provide adequate evidence, justifying the efforts in health care to collect the data, registers need to have both acceptable coverage and a set-up including the relevant variables.

Interestingly, the two studies using propensity score matching focused on cardiovascular disease, illustrating that researchers within this therapeutic field are often pioneers when it comes to methodological advancements, as was the case when randomized controlled design was introduced. Indeed, although propensity score matching was introduced several years ago [36], this technique seems to have undergone limited divergence within the academic world. Some articles using propensity scores for adjustments were also identified [18, 34], although such applications are controversial [36].

Another approach to minimize confounding is to make intra-individual comparisons, as in the studies on the effects of antipsychotics [19] and ADHD medications [15, 16, 23]. However, a patient's health condition, including their psychiatric status, may vary over time and be associated with drug treatment adherence, and this is consequently a limitation of this technique.

In randomized controlled studies, intention-to-treat analyses are often preferred as they reflect the clinical situation to a greater extent, and give a more realistic picture on what to expect upon prescribing a drug. In fact, this is an accepted approach as it introduces a systemic error which makes it harder to reach a specified end point. Our review shows that this technique has been adopted in almost half of the effectiveness studies included. However, in clinical practice the compliance is much lower than in well-monitored clinical trials with selected patients and thorough follow-up. Therefore, misclassification due to lack of compliance or change of treatment can be expected to be considerably greater in an epidemiological study. Consequently, the intention-to-treat

approach may be less appropriate in this setting. Further, methodologically suboptimal assumptions concerning drug exposure were identified, an acknowledged challenge in pharmacoepidemiology [37]. Therefore, involving researchers with pharmacoepidemiological skills may be valuable in the authoring and reviewing processes of effectiveness studies.

Performing sensitivity analyses, as done to various extents in half of the publications, is an illustrative way of handling uncertainties when making assumptions and evaluations in effectiveness studies based on register data. These analyses can reflect several aspects of uncertainty, including population studied, exposure estimations, outcome measured and missing data.

The methodological problem of immortal time bias [38] was identified in a few of the reviewed effectiveness studies. Another pitfall, which is relatively easy to handle, was that no publication in this review stated that it was guided by a predefined protocol describing the statistical analyses and defining the size of a clinically meaningful difference between the comparison groups. As register data can be obtained for a large number of individuals, more attention needs to be drawn to clinical relevance, rather than power calculations being done. Encouragingly, protocols for effectiveness studies seem to emerge in the scientific literature [39], illustrating a positive trend in this area.

As the results of effectiveness studies are largely dependent on the methodology used, it is reassuring that public funding exists within the field. Indeed, although associations between study conflicts of interest and effect sizes have not been found in randomized controlled trials [40, 41], effectiveness studies may be more sensitive to this type of bias, as the methodological alternatives are numerous and harbour biases to various extents. Thus, knowledge and awareness of methodological issues is essential when interpreting results of effectiveness studies. In the present review, although the publications funded by the pharmaceutical industry focused on therapeutic areas with new treatment alternatives, none of these studies contributed new knowledge on intended drug effects.

Strengths and limitations

An important strength of the present study is that it starts off from a comprehensive review of the output of the SPDR, using several strategies to identify relevant publications. Indeed, drug effectiveness studies may be identified only to a limited extent in literature searches. Further, the assessments were performed independently by two clinical pharmacologists with experience in evidence-based decision making, both at the patient and at the societal level, with good inter-rater agreement.

The fact that we have focused on Swedish studies using SPDR may be regarded as a limitation affecting the generalizability of the results. However, this country may be considered a gold mine for drug effectiveness studies because of its numerous linkable, nationwide and individual-based registers of high quality. Further, the methodologies can be expected to be advanced because Sweden has a long tradition of epidemiological studies [9], which is illustrated by the fact that several articles were published in the highest ranked

scientific journals. Nevertheless, the SPDR is a relatively new data source, and methodology can be expected to evolve over time. Because of the limited material in the present study, the time factor has not been assessed.

Conclusions and implications

In the present study, we show that drug effectiveness studies, based on register data collected in a non-interventional setting, can contribute, but seldom do, to new knowledge on intended beneficial drug effects. Indeed, the problems of published studies regarding scientific quality ought to moderate the prevailing expectations that registers will provide the drug effectiveness data needed for decision making. To take advantage of the opportunities offered by the increasing availability of data, researchers and decision makers need to be aware of both pitfalls and good practice, bearing in mind the importance of having access to relevant data, using sound designs and methods, as well as reporting the results in an adequate way.

Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors

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

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