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REVIEW

Sensitivity of Cost-Effectiveness to Inclusion of Adverse Drug Events: A Scoping Review of Economic Models of Pharmacological Interventions for Diabetes, Diabetic Retinopathy, and Diabetic Macular Edema

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Purpose: Incorporation of adverse drug events (ADEs) is suboptimal in economic evaluation, and thus the information provided by it may be inaccurate. Better guidance on incorporating ADEs into economic evaluation prompts for exploring whether the results are sensitive to ADEs.

Methods: This scoping review explored 242 cost-effectiveness models for pharmacological interventions for type 1 (T1DM) and 2 diabetes (T2DM), diabetic retinopathy (DR), and diabetic macular edema (DME), in relation to the type of ADEs included in the models (if any), whether the results were sensitive to the ADEs, and what could explain their potential impact.

Results: Of the analyses partly or completely including ADEs, 62% examined their impact on the results, with half of them (50%) reporting ADE-related sensitivity. The models included common to very common ADEs, and some rare but severe ones. The main reasons for excluding ADEs were low incidence (13%) and no reporting in clinical trials (13%). Many analyses reported no reason for the exclusion (53%). The analyses for T1DM and DR or DME included more severe ADEs and reported a higher ADE-related sensitivity compared to the analyses of T2DM (76,2%, 77.8%, and 46.4%, respectively). Higher incidence of ADEs (60,0%) and time trade off method (72,2%) were associated with higher ADE-related sensitivity (72,2%).

Conclusion: Incidence, condition, and the measure of utility were associated with the results being sensitive to ADEs. ADEs are an important outcome for the results of economic evaluation and better guidance on their inclusion and exclusion is needed.

Keywords: economic evaluation, modeling, complications, adverse event

Introduction

Adverse drug events, ADEs, are harmful outcomes associated with pharmaceutical interventions. These events relate to any unintended or unexpected incident that could have or did lead to harm for patients receiving the drug therapy. ADEs are not necessarily related to the pharmaceutical intervention itself, rather they can be related to anything within the medication process. Adverse drug reactions (ADRs), however, are always causally related to the pharmaceutical intervention in question.[1–3] ADEs impact both treatment costs and treatment effectiveness. The costs arise from additional treatment of ADEs, such as medication, procedures, hospitalizations, or monitoring. The impact on effectiveness is due to, for example, discontinuation of the treatment due to ADEs, or the symptoms impacting quality of life, such as pain, discomfort, and fear.

The regulatory documentations, such as the summary of product characteristics (SmPC) for pharmaceuticals, entail the incidence and severity of ADEs that, by definition, are causally related to the pharmaceutical intervention. The groupings for the incidence are using the following conventions: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000

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to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). This means, for example, that if at least one patient out of ten experiences an ADE, the ADE is considered very common.[4]

Regarding severity, ADEs have four groupings for their intensities: mild, moderate, serious, and severe, also described by grades ranging from 1 to 5 (1 being mild event and 5 indicating for death).[5,6] Serious ADEs lead to death or significant disability, are life-threatening, or require/prolong inpatient hospitalization.[7,8] Severe ADEs are merely strong in their intensity, and, therefore, an ADE can be non-serious but severe, such as a headache. Any harm, even a minor one, may be important from a patient's perspective, especially with ADEs that constantly recur and/or last for a longer period. The impact on a patient's quality of life could be harmful even if the harms are not considered serious or severe.[9]

Data on ADEs collected during randomized clinical trials (RCTs) forms the basis for subsequent safety and efficacy analyses of pharmaceuticals. The guideline for reporting of harms in randomized trials (The Consolidated Standards of Reporting Trials (CONSORT) Harms 2022 Statement) states that RCTs should carefully identify and define both the harms that are systematically collected via, for example, medical examination and questionnaires, and the harms that are non-systematically collected via unprompted self-reporting by patients. The guideline strongly recommends that thresholds for reported harms would not be applied, instead, RCTs should provide a summary of the data of harms in the main report and report all the details related to harms. Any criteria for selecting the harms for reporting should always be prespecified and stated explicitly.[9] The recommendations from MPIP (Medical Publishing Insights & Practice – partnership among pharmaceutical companies and the International Society for Medical Publication Professionals) for improving adverse event reporting in clinical trial publications differ from CONSORT Harms 2022 Statement and are not as precise since the recommendation highlights the importance of reporting the most clinically relevant ADEs and clearly stating the rationale for focusing on the selected ADEs. The reporting of ADEs should include timing, frequency, duration, and the method of collection (systematic or non-systematic).[10]

Despite the guidelines, the collection, reporting, and analysis of adverse events in clinical trials seem to be inconsistent. A recent review of RCTs published in high impact journals found that 62% of RCTs reported some form of spontaneous adverse event collection, but only 29% of the RCTs reported adverse event collection with more specific details.[11] Similar results for poor reporting of ADEs in clinical trials have been reported in other reviews, as well.[12,13] Non-randomized studies of interventions such as cohort studies and case–control studies may provide data on long-term and rare ADEs compared to RCTs, although non-randomized studies tend to entail a greater risk of bias.[14]

Economic evaluation is a framework for providing evidence for comparing competing courses of action in terms of their benefits obtained against the resources consumed. Economic evaluation aims to determine whether the technology is worth funding given its consequences (benefits and harms) and the resources it requires,[15,16] that is, whether the technology is good value for money. Cost-utility- and cost-effectiveness analyses are common types of economic evaluation usually using modeling methods in defining economic value of pharmaceutical interventions. A model is a simplified representation of reality combining and extrapolating different types of data in order to estimate long-term costs and consequences. Effectiveness data can be collected through the standard methods of clinical outcomes research, namely RCTs and observational studies. The measure of effectiveness in cost-effectiveness analysis is often quality-adjusted life years (QALYs) that is a generic measure for health benefit and as a numerical indicator it combines mortality and morbidity into a single index number, consequently including a combination of quantity (longevity/mortality) and health-related quality of life (HRQoL). This combination is based on the relative desirability of different outcomes; thus, the numerical indicator represents preferences, ie, utilities, for different health states. The quality of effectiveness data is the basis for economic evaluation of good quality.[16]

The modeling practices seem incomplete in terms of criteria and the means by which ADEs are addressed in the modeling. The guidelines for health technology assessment (HTA) and recommendations for best practices for modeling generally consider ADEs as an important outcome and outline that effectiveness and harms associated with the intervention should be accounted for in economic evaluation. Despite this, the guidelines are generally somewhat vague in terms of practically guiding the incorporation of ADEs into the modeling as they usually merely state that ADEs are relevant to consider in the analysis but provide no further guidance.[17–22] For example, when the EUnetHTA guidelines for relative safety assessment consider the importance of identification of ADEs and their quantification in terms of frequency, incidence, severity, and seriousness,[23] the EUnetHTA guidelines for methods of economic evaluation provide no guidance on incorporation of ADEs in economic evaluation.[24] Some guidelines for economic evaluation

elaborate more on ADEs, highlighting a need for increased focus on the harms that are clinically meaningful, with a particular attention to the frequency, duration, and severity of ADEs, as well as the expected sensitivity of the cost-effectiveness results to the ADE-related impact on health state utilities.[25–27] Nevertheless, no standardized methods related to the inclusion of ADEs in economic evaluation of health technologies currently exist.[28]

It is seemingly variable how economic models consider ADEs. One of the first research concerning ADEs in economic evaluation was the work of Craig et al[29] who examined a sample of HTA-reports and the inclusion of ADEs in the analyses. They concluded that only 54% of the decision models in health technology assessments included adverse effects, and with a varying manner in clinical and cost parameters. Consequently, similar findings are available with regard to ADEs in economic evaluation for cancer treatments.[30–32] A recently published scoping review of cost-effectiveness models for diabetes and diabetic conditions[33] revealed that 26% of the included cost-effectiveness analyses comprehensively included ADEs, and 13% of the analyses excluded them. Most of the analyses (61%) only considered one or two ADEs, thus partly including ADEs in the analyses.

Despite existing guidelines for collecting ADEs and incorporating them in economic evaluation, the practices seem to be diverging. Determining which ADEs should be included in modeling-based cost-effectiveness analyses and how they should be included requires a better understanding of the potential impact of ADEs on the results of the analysis. Only by understanding the meaningfulness of ADEs in the context of the results it is possible to build criteria on inclusion of ADEs in cost-effectiveness analyses.

Review Question(s)

The objective of this scoping review is to further explore the incorporation of ADEs in cost-effectiveness models for type 1 and 2 diabetes, diabetic retinopathy, and diabetic macular edema using the same dataset used in a published scoping review.[33] The aim now is to investigate what types of ADEs are included in the cost-effectiveness models, whether the inclusion of ADEs seems to have an impact on the results of the analysis, and what could explain the possible impact. Based on these insights, we aim to draw conclusions on the selection criteria and the modeling methods of ADEs in cost-effectiveness analyses for the future.

The research questions in this scoping review are:

1. Did the models that included ADEs examine the ADE-related impact on the results of the analysis?
2. What type of ADEs were included in the cost-effectiveness models in terms of incidence, severity, and seriousness, and what type of ADEs were excluded and why?
3. Did the inclusion of ADEs impact the results of the analysis?
4. What might explain the impact or no impact to the results?

Material and Methods

This review included two sets of data that were combined for analyzing the research questions.

Data Set 1

The first data set used a published data set of a scoping review[33] which consisted of published cost-effectiveness- and cost-utility analyses for pharmacological interventions indicated for types 1 and/or 2 diabetes (T1DM and/or T2DM), and their complications: diabetic retinopathy (DR) or diabetic macular edema (DME). The data set 1 excluded all other conditions and pharmacological therapies indicated for other conditions. The included cost-effectiveness and cost-utility analyses had to apply a modeling framework and evaluate at least one pharmacological intervention. Other types of economic evaluation, such as cost–benefit analyses, were excluded. The included cost-effectiveness analyses had to report incremental cost-effectiveness ratio (ICER) as cost per quality-adjusted life-year (QALY) since this is the most used outcome for economic evaluations of pharmaceuticals.

The data set 1 included published journal articles from several databases (namely: MEDLINE (PubMed), CINAHL (EBSCOhost), Scopus, Web of Science, Core Collection and NHS Economic Evaluation Database), and sources of grey literature (that is; the National Institute for Health and Care Excellence (NICE), European Network for Health

Technology Assessments (EUnetHTA), and International HTA database (INAHTA) technology appraisals). Systematic reviews and scoping reviews were "hand searched" to identify published cost-effectiveness or cost-utility analyses matching the inclusion criteria. Only studies published in English from January 1, 2011, to December 31, 2022, were included in the data set.

In total, 13,003 records were identified from the databases. After removing duplicates (5958), a total of 7045 records were screened. At full-text review, 340 reports were retrieved with 237 studies included for the data set 1. Additionally, the hand-search of the review articles led to inclusion of 5 reports to the data set 1. Ultimately, a total of 242 studies were included in the data set 1. The search results, study selection, and inclusion process are described in more detail in Appendix 1. Descriptions of the included databases, search strategy and results, and data extraction are also available in published sources.[33,34]

The data set included information related to if and how ADEs were included in the models. An analysis was concluded to include ADEs if more than two of the ADEs mentioned in the efficacy studies and/or SmPC were considered. If one or two of the possible ADEs were included and other possible ADEs omitted, the analysis was considered to partly include ADEs. Additionally, some analyses excluded all the ADEs. The data set included information on, for example, which ADEs were included, were the ADEs included in cost- and/or utility-estimates, the sources of these inputs, and whether the impact of ADEs was examined in relation to the results of the analysis.

Data Set 2

The second data set included information on which ADEs related to pharmacological treatments for the conditions are reported in SmPCs.[35–64] The pharmacological treatments of diabetes included glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide, liraglutide, dulaglutide, exenatide, lixisenatide), sodium-glucose transport protein 2 (SGLT-2) inhibitors (empagliflozin, dapagliflozin, canagliflozin), insulins (insulin degludec, insulin glargine, insulin detemir, NPH-insulin, insulin degludec/insulin aspart, insulin degludec/liraglutide, biphasic insulin aspart/Premix BIAsp 30, insulin Lispro), DPP-4-inhibitors (alogliptin, linagliptin, sitagliptin, saxagliptin), pioglitazone, sulfonylureas, tirtzepatide, and acarbose. For diabetic macular edema, the pharmacological treatment options included intravitreal corticosteroid implants or injections (triamcinolone, dexamethasone, fluocinolone) and anti-vascular endothelial growth factor (anti-VEGF) injections (aflibercept, bevacizumab, ranibizumab). A wide range of ADEs are related to these pharmacological treatments, some of them being less severe and common (eg, nausea and diarrhea), and some of them being severe and rare (eg, endophthalmitis). The definition of ADE incidence is based on available SmPCs and the classification of their severity is based on Common Terminology Criteria for Adverse Events (CTCAE).[6] Hypoglycemia is commonly reported as an ADE of the pharmacological treatments for diabetes, although hypoglycemia is also a complication of diabetes itself. The included interventions and their wide range of ADEs with their grade of severity and incidence are presented in Appendix 2.

Data Analysis and Presentation

The study inclusion process for the first data set is presented in the form of a PRISMA flow diagram (Appendix 1), and the characteristics of all included studies are presented in a published study[33] Different parts of the data set are separately examined to answer the research questions of this scoping review. First, the analyses that either completely or partly included ADEs are explored in terms of which ADEs were included and how the inclusion corresponds to the information presented in the SmPCs, as presented in the second data set of this scoping review (Appendix 2). Secondly, the analyses excluding ADEs are examined to understand the reasons for the exclusion.

Finally, of the analyses that at least partly included ADEs, those reporting the impact of ADEs to the results were reviewed to identify if the results were sensitive to ADEs and the reasons potentially explaining the impact. If the analyses reported results being sensitive to ADEs, that was considered as a meaningful impact on the results. This analysis was done descriptively since a scoping review as a methodology contains no statistical data-analytics.

Flow diagram is used to present the different parts of the data set that are separately analyzed per research question. The rest of the results are presented in a tabular format.

Results

A total of 242 analyses were initially included in the first data set (Appendix 1). Of these, 210 (87%) either completely or partly included ADEs ("partly" meaning that only one to two ADEs were included, although more applicable existed), and 32 (13%) excluded them. The characteristics of the included studies (eg, year of publication, type of model, time horizon) are presented in a published scoping review.[33] Of the 210 analyses that at least partly included ADEs, 130 (62%) examined the ADEs impact on the results of the analysis, as 80 (38%) did not (Figure 1).

The included ADEs for type 1 and type 2 diabetes models were most often hypoglycemia (T1DM: 100%, T2DM: 97%), weight gain (T1DM: 13%, T2DM: 19%), and urinary tract infection (T1DM: 4%, T2DM: 17%). The severity of hypoglycemia varies, as grade 1 hypoglycemia only impacts laboratory test values, but, for example, grade 4 causes life-threatening consequences. The included studies in this review had a variable reporting for hypoglycemia. Some studies made differentiation between minor and severe hypoglycemia, and some reported hypoglycemia irrespective of the grade. Therefore, hypoglycemic events in the included analyses range from mild (grade 1) to severe (grade 4). Weight gain is considered mild (grade 1) if the change in weight ranges from 5% to 10% from the baseline. The included models in this review did not define the magnitude of the weight gain. The grade of urinary tract infection ranges from grade 2 to grade 4, normally being treated with medication, thus corresponding to grade 2. Some of the analyses, especially for T1DM, also included diabetic ketoacidosis (T1DM: 13%, T2DM: 4%) that is an ADE of grade 4, and some analyses for T2DM (8%) included nausea and gastrointestinal events, ranging from grade 1 to 2.[6]

The included ADEs for DR and DME most often were cataract (83%), retinal detachment (72%), and endophthalmitis (61%). Additionally, the models for DR and DME included systemic ADEs such as stroke (28%) and myocardial infarction (17%). All these ADEs are commonly moderate-to-severe ADEs. The included ADEs and their respective grading are presented in Table 1.

In general, the models rather well included ADEs that were classified as "very common" or "common" in the SmPCs. The rare ADEs reported in the SmPCs, such as acute pancreatitis, angioedema, or limb amputations, were characteristically excluded in the cost-effectiveness models included in this review, with some exceptions with serious rare ADEs, such as endophthalmitis and diabetic ketoacidosis, that the models accounted for. The classification of ADEs in terms of their incidence as outlined in SmPCs is presented in Appendix 2.

Of the analyses that excluded ADEs (n=32, 13%) the main reasons for the exclusion were low incidence of ADEs (13%), lack of reporting in clinical trials (13%), no difference in the incidence between the treatments in comparison

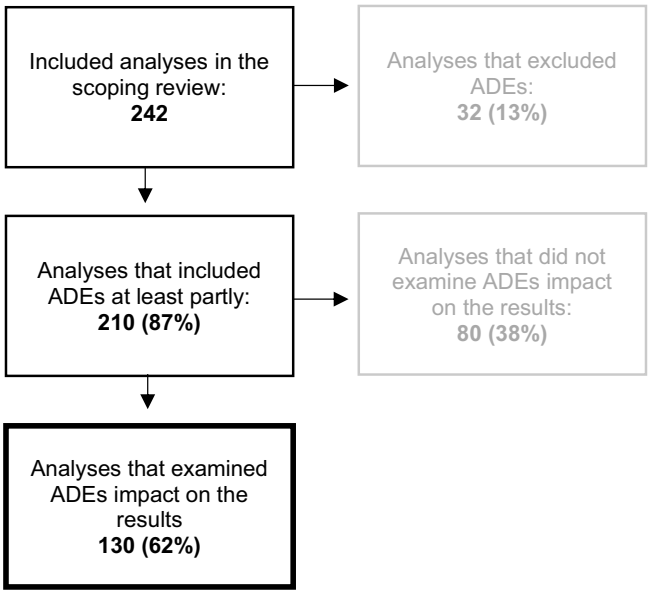

Figure 1 Included analyses in the review.

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Table 1 Included ADEs With Their Grading in T1DM, T2DM, DR, and DME Model

ADE	Grade*	T1DM	Share, %	T2DM	Share, %	DR/DME	Share, %
T1DM and T2DM related ADEs							
Hypoglycemia	1 to 4	23	100,0%	176	97,2%	0	0,0%
UTI	2	1	4,3%	30	16,6%	0	0,0%
Nausea	1 to 2	0	0,0%	14	7,7%	0	0,0%
Genital infection	2	0	0,0%	34	18,8%	0	0,0%
Weight gain	1	3	13,0%	34	18,8%	0	0,0%
Vomiting	2	0	0,0%	3	1,7%	0	0,0%
Diarrhea	1 to 2	0	0,0%	1	0,6%	0	0,0%
Gastrointestinal events	1 to 2	0	0,0%	10	5,5%	0	0,0%
Headache	1 to 2	0	0,0%	1	0,6%	0	0,0%
Upper respiratory tract infection	2	0	0,0%	1	0,6%	0	0,0%
Nasopharyngitis	2	0	0,0%	1	0,6%	0	0,0%
Injection reaction	1	0	0,0%	3	1,7%	0	0,0%
Diabetic Ketoacidosis	4	3	13,0%	7	3,9%	0	0,0%
Kidney injury / failure	3 to 4	0	0,0%	3	1,7%	0	0,0%
Bone fracture	2	0	0,0%	1	0,6%	0	0,0%
Amputation	4	0	0,0%	1	0,6%	0	0,0%
DR/DME related ADEs							
Stroke / cerebrovascular accident / arterial thromboembolic events	2 to 4	0	0,0%	0	0,0%	5	27,8%
Myocardial infarction	2 to 4	0	0,0%	0	0,0%	3	16,7%
Cataract	2 to 4	0	0,0%	0	0,0%	15	83,3%
Glaucoma	1 to 4	0	0,0%	0	0,0%	8	44,4%
Endophthalmitis	2 to 4	0	0,0%	0	0,0%	11	61,1%
Retinal detachment	3 to 4	0	0,0%	0	0,0%	13	72,2%
Vitreous hemorrhage	1 to 3	0	0,0%	0	0,0%	10	55,6%
IOP rise	1 to 2	0	0,0%	0	0,0%	7	38,9%

Notes: *Grading based on Common Terminology Criteria for Adverse Events (CTCAE).

(9%), and ADEs being transient events not impacting inpatient costs (9%). Half of the analyses that excluded ADEs did not specify the reason for the exclusion (53%) (Table 2).

The 130 analyses that completely or partly included ADEs in the model and examined ADEs' impact on the results showed varying influence of ADEs. The impact of ADEs on the results of the analysis is presented in Table 3.

Considering all the conditions (T1DM, T2DM, DR, and DME) together, half (50%) of the analyses showed ADE-related sensitivity to the results, and the other half only a minor or no impact at all (data not shown). The sensitivity of the results was rather independent of whether both ADE-related disutilities and costs or only disutilities, or only costs were included (50%, 50%, 63%, respectively). The analyses for T1DM and DR or DME more often reported ADEs having a meaningful impact on the results (76% and 78%, respectively) compared to the analyses for T2DM (46%). Most of the analyses for T1DM and T2DM only partly included ADEs (20 (95%) and 87 (78%), accordingly) and overall

Table 2 Reasons for Excluding ADEs

Reasons for Exclusion	n = 32
No difference in incidence between comparators	3 (9%)
Low incidence	4 (13%)
Assumed negligible impact	1 (3%)
Transient events causing no inpatient costs	3 (9%)
Not reported in the clinical trial	4 (13%)
Reason not specified	17 (53%)

Table 3 The Impact of ADEs to the Results of the Analysis

	ADEs Had Impact	ADEs Had Minor Impact/No Impact
T1DM		
Yes or partly (n=21)	**16 (76,2%)**	**5 (23,8%)**
DUs* and costs* (n=19)	15 (78,9%)	4 (21,1%)
DUs*and no/unclear costs (n=1)	1 (100,0%)	0 (0,0%)
Costs* and no/unclear DU (n=1)	0 (0,0%)	1 (100,0%)
Unclear costs and unclear DU (n=0)	–	–
Yes (n=1)	0 (0,0%)	1 (100,0%)
DUs* and costs* (n=1)	0 (0,0%)	1 (100,0%)
DUs*and no/unclear costs (n=0)	0 (0,0%)	0 (0,0%)
Costs* and no/unclear DU (n=0)	0 (0,0%)	0 (0,0%)
Unclear costs and unclear DU (n=0)	–	–
Partly (n=20)	16 (80,0%)	4 (20,0%)
DUs* and costs* (n=18)	15 (83,3%)	3 (16,7%)
DUs*and no/unclear costs (n=1)	1 (100,0%)	0 (0,0%)
Costs* and no/unclear DU (n=1)	0 (0,0%)	1 (100,0%)
Unclear costs and unclear DU (n=0)	–	–
T2DM		
Yes or partly (n=112)	**52 (46,4%)**	**60 (53,6%)**
DUs* and costs* (n=99)	46 (46,5%)	53 (53,5%)
DUs*and no/unclear costs (n=10)	5 (50,0%)	5 (50,0%)
Costs* and no/unclear DU (n=2)	1 (50,0%)	1 (50,0%)
Unclear costs and unclear DU (n=1)	0 (0,0%)	1 (100,0%)
Yes (n=25)	9 (36,0%)	16 (64,0%)
DUs* and costs* (n=23)	7 (30,4%)	16 (69,6%)
DUs*and no/unclear costs (n=2)	2 (100,0%)	0 (0,0%)
Costs* and no/unclear DU (n=0)	–	–
Unclear costs and unclear DU (n=0)	–	–
Partly (n=87)	43 (49,4%)	44 (50,6%)
DUs* and costs* (n=76)	39 (49,4%)	37 (50,6%)
DUs*and no/unclear costs (n=8)	3 (37,5%)	5 (62,5%)
Costs* and no/unclear DU (n=2)	1 (50,0%)	1 (50,0%)
Unclear costs and unclear DU (n=1)	0 (0,0%)	1 (100,0%)
DR and DME		
Yes or partly (n=9)	**7 (77,8%)**	**2 (22,2%)**
DUs* and costs* (n=4)	3 (75,0%)	1 (25,0%)
DUs*and no/unclear costs (n=0)	–	–
Costs* and no/unclear DU (n=5)	4 (80,0%)	1 (20,0%)
Unclear costs and unclear DU (n=0)	–	–
Yes (n=7)	5 (71,4%)	2 (28,6%)
DUs* and costs* (n=4)	3 (75,0%)	1 (25,0%)
DUs*and no/unclear costs (n=0)	–	–
Costs* and no/unclear DU (n=3)	2 (66,7%)	1 (33,3%)
Unclear costs and unclear DU (n=0)	–	–
Partly (n=2)	2 (100%)	0 (0,0%)

(*Continued*)

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Table 3 (Continued).

	ADEs Had Impact	ADEs Had Minor Impact/No Impact
DUs* and costs* (n=0)	–	–
DUs*and no/unclear costs (n=0)	–	–
Costs* and no/unclear DU (n=2)	2 (100,0%)	0 (0,0%)
Unclear costs and unclear DU (n=0)	–	–

Notes: *Entirely or partly.

included both the ADE-related impact on quality-of-life estimates and costs (19 (91%) and 99 (88%), respectively). Conversely, the analyses for DR or DME more often completely included ADEs (7 (78%)) and either included both the ADE-related impact on costs and quality-of-life -estimates (4 (44%)) or only in cost estimates (5 (56%)), which appeared to have little influence on the results. Unclear costs and/or disutility meant that the publication did not explicitly state if ADE-related costs or disutilities were included in the model, even if ADEs were reported to be included in the model. Additionally, the included ADEs in the models for T1DM, DR, and DME were more often of higher severity grade compared to the ADEs included in the models for T2DM (Table 1).

Sensitivity due to ADEs was reported to be related to their incidence, impact on utility, or impact on costs. Most often. incidence was mentioned when the sensitivity of the results of the analysis was examined. For all the analyses, incidence usually had a meaningful impact on the results (60%) compared to ADE-related impact on utility (33%) or costs (37%) which more often were considered to have a minor impact or no impact on the results. This was especially seen in analyses for T2DM, as the analyses for T1DM and DR/DME often also reported ADE-related impact on utility or costs to be meaningful in terms of the results of the analysis (Table 4).

The analyses with older publication years (2011–2016) reported slightly more ADE-related sensitivity to the results compared to the analyses with newer publication years (2017–2022). No trend related to the time horizon of the model was observable, although the models with a time horizon of 1 year or less and a time horizon of 10 to 30 years more frequently reported ADEs impacting the results of the analysis (79% and 67%, respectively). The study perspective (health care payer vs societal) of the analysis had no importance in ADEs impacting the results.

Table 4 The Impact of ADE-Related Incidence, Utility, or Costs to the Results of the Analysis, per Condition

	Incidence	Utility	Costs
All conditions (n=*130*) *(ADEs fully or partly included)*	88	57	30
Had impact	53 (60%)	19 (33%)	11 (37%)
Had minor impact / no impact	35 (40%)	38 (67%)	19 (63%)
T1DM (n=*21*)	**20**	**4**	**5**
Had impact	15 (75%)	2 (50%)	2 (40%)
Had minor impact / no impact	5 (25%)	2 (50%)	3 (60%)
T2DM (n=*12*)	**76**	**54**	**24**
Had impact	44 (58%)	15 (28%)	8 (33%)
Had minor impact / no impact	32 (42%)	39 (72%)	16 (67%)
DR and DME (n=*9*)	**4**	**2**	**4**
Had impact	4 (100%)	2 (100%)	2 (50%)
Had minor impact / no impact	0 (0%)	0 (0%)	2 (50%)

Small differences between model types were apparent as Markov-models and semi-Markov models rather often reported ADE-related sensitivity (59% and 57%, respectively) but simulation models less often (40%). Interestingly, all (100%) microsimulation models that examined ADEs impact on the results reported a meaningful impact. Additionally, when ADEs were included as probabilities or risk equations, the results were most often sensitive to ADEs (61% and 67%, respectively) (Table 5).

The patient reported outcome measure (PROM) seemed to be important in terms of ADEs impacting the results of the analysis since 72% of the analyses with time trade off (TTO)-method as a PROM reported ADEs impacting the results of the analysis compared to, for example, analyses using the EQ-5D -method (46%). TTO-method was used rather equally

Table 5 The Role of Other Attributes to the ADE-Related Impact on the Results of the Analysis

	ADEs Had Impact	**ADEs Had Minor Impact/No Impact**
Year of publication (n=130)		
2011 (n=7)	3 (42.9%)	4 (57.1%)
2012 (n=9)	6 (66.7%)	3 (33.3%)
2013 (n=6)	4 (66.7%)	2 (33.3%)
2014 (n=6)	3 (50.0%)	3 (50.0%)
2015 (n=9)	7 (77.8%)	2 (22.2%)
2016 (n=10)	8 (80.0%)	2 (20.0%)
2017 (n=15)	8 (53.3%)	7 (46.7%)
2018 (n=15)	7 (46.7%)	8 (53.3%)
2019 (n=22)	11 (50.0%)	11 (50.0%)
2020 (n=13)	5 (38.5%)	8 (61.5%)
2021 (n=12)	2 (16.7%)	10 (83.3%)
2022 (n=6)	1 (16.7%)	5 (83.3%)
Study perspective (n=130)		
Health care payer (n=113)	54 (47.8%)	59 (52.2%)
Societal (n=14)	8 (57.1%)	6 (42.9%)
Health care payer and societal (n=2)	2 (100.0%)	0 (0.0%)
Private health care payer (n=0)	N/A	N/A
Provider (n=0)	N/A	N/A
Unknown (n=1)	1 (100.0%)	0 (0.0%)
Time horizon		
≤1 year (n=19)	15 (78.9%)	4 (21.1%)
>1 year and <10 years (n=4)	1 (25.0%)	3 (75.0%)
≥10 years and ≤30 years (n=12)	8 (66.7%)	4 (33.3%)
>30 years (n=95)	41 (43.2%)	54 (56.8%)
Model type		
Simulation model (n=78)	31 (39.7%)	47 (60.3%)
Markov model (state-transition model) (n=17)	10 (58.8%)	7 (41.2%)
Microsimulation model (n=5)	5 (100.0%)	0 (0.0%)
Semi-Markov model* (n=7)	4 (57.1%)	3 (42.9%)
Discrete event simulation model (n=5)	2 (40.0%)	3 (60.0%)
Decision tree (n=0)	N/A	N/A
Partitioned survival model (n=0)	N/A	N/A
No specification (n=18)	13 (72.2%)	5 (27.8%)

(*Continued*)

Table 5 (Continued).

	ADEs Had Impact	ADEs Had Minor Impact/No Impact
Method for ADE inclusion		
Probability (n=70)	43 (61.4%)	27 (38.6%)
Sub-model (n=48)	15 (31.3%)	33 (68.8%)
Sub-model and probability (n=8)	5 (62.5%)	3 (37.5%)
Separate health state (n=1)	0 (0.0%)	1 (100.0%)
Risk equation (n=3)	2 (66.7%)	1 (33.3%)
PROM used in the model		
EQ-5D (n=91)	42 (46.2%)	49 (53.8%)
TTO (n=11)	8 (72.7%)	3 (27.3%)
SG (n=1)	0 (0.0%)	1 (100.0%)
HUI3 (n=1)	1 (100.0%)	0 (0.0%)
Unknown (n=26)	14 (53.8%)	12 (46.2%)

Notes: *Semi-Markov: Elements of Markov model and other types of models.

often in T1DM-models (n=3, 21%) and T2DM-models (n=4, 29%) but more frequently in the models for DR or DME (n=7, 50%) (see Appendix 3). Furthermore, the PROM used to measure ADE-related disutilities was not always the same measure as the PROM used for measuring HRQoL related to other clinical events and health states in the modeling, and sometimes, even a different PROM was used to measure different disutilities related to different ADEs.[33]

Discussion

The cost-effectiveness analyses in this review considered the sensitivity of the results to ADEs in a varying manner. As often as this was examined, it was commonly also disregarded.

Also, the sensitivity of the results to ADEs considerably varied, with the most prominent factor of influence being the condition as 76% of the models for T1DM, 46% for T2DM, and 78% for DR or DME reported meaningful impact of ADEs on the results. The ADE-related sensitivity, therefore, was noticeably lower in models for T2DM. Usually, the severity grade of ADEs in the analyses for T2DM was mild to moderate, as the analyses for T1DM and DR or DME often included moderate-to-severe ADEs. The severity of the included ADEs could be the underlying factor behind the difference in ADE-related sensitivity between the conditions since the more severe the ADE, the more significant impact they have on quality of life and treatment costs.

Generally, the analyses included ADEs that were classified as common to very common. Incidence of ADEs was the most frequently reported attribute of ADEs impacting the results of cost-effectiveness analyses, especially in the models for T2DM. Since in practice, the incidence of ADEs is modelled through utilities and/or costs, the incidence potentially includes the impact of both ADE-related disutility and ADE-related costs thus could therefore impact the results more than ADE-related utilities or costs alone. Nevertheless, the impact of the incidence of ADEs could indicate that the impact is caused by the number of events irrespective of the severity of the event. Regarding the models for T1DM and DR or DME, also ADE-related disutility seemed important, although in this category the number of analyses was rather low. The quality-of-life decrement related to ADEs was often measured with different PROM compared to the PROM used for the model in general. For instance, if the PROM applied in the model was EQ-5D, the disutilities related to ADEs could have been derived via, for example, TTO-method, Index of Well-being, or SG-method.[33] This contradicts with the guidelines for economic evaluation that state that utility data on all health states should use the same preference-based measure.[27]

In addition to disutilities, the health state utilities in general seemed to influence ADE-related sensitivity of the results, as models using the TTO-method as a PROM most often reported ADEs impacting the results. A higher share of analyses for DR and DME obtained utilities using the TTO-method; hence, it remains unclear whether the condition explains the impact related to the TTO-method or whether it is the measure of health-related quality of life itself (Appendix 3).

According to this review of cost-effectiveness analyses, the three characteristics – incidence, condition, and health-related quality of life – seemed to be the main causes of influence of ADE-related sensitivity of the results. The guidelines for economic evaluation generally consider severity, incidence, frequency, duration, and expected impact on health state utilities as important aspects of ADEs.[24,26,28] Of these characteristics, the frequency and duration of ADEs as such were not examined in this scoping review nor were they mentioned in the included cost-effectiveness models as important characteristics of ADEs in terms of the sensitivity of the results. Frequency and duration of ADEs, however, are implicitly important characteristics of ADEs, since, for example, a mild ADE might become more disturbing if it lasts for a long time or frequently repeats over time. Also, the duration of ADEs is needed when estimating the ADE-related impact on health state utility, that is, for how long a period the ADE-related utility decrement lasts.

Noteworthy is that around half of the analyses (53%) in this scoping review that excluded ADEs from the analysis omitted the rationale for the exclusion, which should always be provided. The analyses that provided the rationale, the most common reasons for not including ADEs in the model were low incidence of ADEs or no difference in the incidence of ADEs between the comparators. Since cost-effectiveness analyses are comparative in nature, exclusion of ADEs can occasionally be justifiable due to these reasons. Quite often the reason of "ADEs not reported in the clinical trial" was also used (13%) as cost-effectiveness models most commonly apply efficacy data from clinical trials. Clinical trials not reporting ADEs, however, do not mean that no ADEs exist, rather this is related to the challenge of clinical trials not thoroughly detecting and reporting ADEs. No clear guidance exists on whether all ADEs or only clinically relevant ones should be reported in clinical trials[9,10] and thus reporting practices have been varying.[11–13] Additionally, the limited follow-up period and selected, often small population may prevent detecting ADEs that are rare and/or occur over time. These shortcomings of clinical trials cause a lack of evidence on ADEs in the data sources used in economic modeling. Moreover, the inputs needed for modeling are sometimes challenging to collect, as, for example, short-term ADEs represent a challenge in health-utility assessment due to practical and potential ethical considerations when requiring patients to complete a questionnaire during an acute episode.[65]

The problem of inconsistent inclusion of ADEs seems to happen at three levels; firstly, the data sources for ADEs (especially clinical trials) are lacking comprehensive collection, reporting, and analysis of ADEs, thus making it too easy for economic modelers to rely on the data provided by these sources and exclude the ADEs based on no evidence reported. Secondly, quantifying the ADEs impact on quality of life (or costs), is not simple since, for example, rarely can health-related quality of life be collected directly from the patients experiencing the ADEs. And thirdly, the guidelines for economic evaluation are lacking explicit instructions for inclusion of ADEs and thereby economic models apply different (arbitrary) criteria for inclusion and exclusion of ADEs. At every level, important information about ADEs is lost, consequently leading to suboptimal inclusion of ADEs in economic models.

Strengths and Limitations

A comprehensive data set, consisting of 242 published cost-effectiveness models for T1DM, T2DM, DR, and DME, was the strength of this large scoping review. The collection of the data set has been carefully designed first by a published protocol[34] and then by a published scoping review.[33]

A scoping review as a methodology aims to map the evidence gaps and is thus exploratory and descriptive in nature.[66] Therefore, considering the research questions 3) and 4) of this review, no statistical analysis with data synthesis was feasible to perform; rather, the analysis was qualitative and descriptive. With descriptive data analysis, we cannot draw explicit conclusions on whether a specific attribute, for example, a disease or a PROM, is truly connected to the ADE-related sensitivity of the results. This was one of the limitations of the chosen methodology. Still, the descriptive results of this review are in line with what has been known so far about the ADE-related characteristics impacting the results of cost-effectiveness analyses.

Another limitation of this review was a lack of details considering the ADE-related characteristics that the results of cost-effectiveness analyses were generally sensitive to. For example, incidence of ADEs was one of the most important characteristics of ADEs impacting the results. The data sources rarely reported any incidence thresholds nor was this information as such extracted for the data set of this review. Therefore, this scoping review cannot give an answer to an appropriate threshold (if any) for the incidence.

Additionally, this review did not cover the impact of ADE-related treatment discontinuation on the results of cost-effectiveness analyses. Discontinuation due to ADEs leads to decreased treatment efficacy as the treatment is prematurely

discontinued. Generally, the efficacy data in cost-effectiveness models is based on intention-to-treat (ITT) analysis of a clinical trial, which includes both the study subjects that completed the trial and those who discontinued. Thus, an ITT-analysis should consider the decreased treatment efficacy due to ADE-related discontinuation. This also relates to the topic of potential double-counting of ADE-related impact on quality of life: If the general health state utility value is based on quality of life collected directly from the study population, it should (in theory) already account for the impact of ADEs. If an additional utility decrement is still applied for the ADEs, that might cause double counting of ADE-related quality of life impact. Then, again, the general measuring of quality of life normally does not happen during an adverse drug event; rather, quality of life is measured during a stable situation, thus it is arguable whether the general health state utility value truly captures the ADE-related impact on quality of life. The potential double counting of ADEs would be an interesting topic to explore further, but the models included in this review did not address this.

Conclusion

Safety outcomes are important factors in the determination of both clinical and economic value of a pharmaceutical intervention. However, information regarding the ADEs is lost at every step; clinical trials fail to detect and report all ADEs, leading to incomplete safety outcome results. Economic evaluations include only some of the ADEs reported in the clinical trials, with practical challenges in assessing the ADE-related impact on quality of life and costs, which leads to insufficient consideration of ADEs in the analysis.

The cost-effectiveness models in this scoping review examined ADE-related sensitivity to the results in a varying manner and the sensitivity of cost-effectiveness analyses to adverse drug events considerably differed. As often as adverse drug events were considered irrelevant to the results of cost-effectiveness analyses, they were also deemed as important events impacting the results of the analysis. Incidence, condition/severity, and health state utilities appeared to be important aspects of ADEs having a potential impact on the results of the analysis, as also stated in the guidelines for economic evaluation. Additionally, the PROM used in the model in general seemed to cause ADE-related sensitivity of the results.

These findings prompt for a better guidance on the inclusion of ADEs to cost-effectiveness models and better justification of their exclusion. Clear criteria and methodological guidance on the inclusion of ADEs in cost-effectiveness analyses might help in reducing the discrepancies related to practical modeling and thus improve the quality of the information provided by economic evaluation.

Disclosure

The authors report no conflicts of interest in this work.

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