Modelling drug-related morbidity in Sweden using an expert panel of physicians

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Title

**MODELLING DRUG-RELATED MORBIDITY IN SWEDEN USING
AN EXPERT PANEL OF PHYSICIANS**

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ABSTRACT

Purpose: In modelling studies using pharmacists' opinion, drug-related morbidity (DRM) and preventable DRM have been more common than in observational studies and the resulting costs are extensive. Modelling studies' estimates may vary depending on informants' profession. The purpose of this modelling study was to estimate the proportion of patients with DRM and preventable DRM and the cost-of-illness (COI) of DRM in Sweden based on physicians' expert opinion.

Method: A conceptual model of DRM was modified from previous studies. Using a modified Delphi technique, a panel of physicians (n=19) estimated the probabilities of DRM, preventable DRM and clinical outcomes of DRM, separately for outpatients and inpatients. DRM included new medical problems (adverse drug reactions, drug dependence and intoxications by overdose) and therapeutic failure (insufficient effects of medicines and morbidity due to untreated indication). A COI analysis included the direct costs of DRM.

Results: Physicians estimated that $51\pm 22\%$ (mean $\pm$ SD) of outpatients experience DRM and $12\pm 8\%$ preventable DRM. Of inpatients, $54\pm 17\%$ was estimated to experience DRM and $16\pm 7\%$ preventable DRM. Of outpatients with DRM, $23\pm 11\%$ was estimated to experience preventable DRM, while this proportion for inpatients was $30\pm 15\%$. The estimated COI was EUR 376 per outpatient and EUR 838 per inpatient.

Conclusions:

Swedish physicians estimated that every other outpatient and inpatient experiences DRM, which is often preventable and costly. As physicians' estimates on the proportion of patients with DRM were higher than in observational studies in restricted sub-populations, DRM may be more common in the general population than observational studies suggest.

KEYWORDS

Drug-related morbidity

Cost of illness

Preventability

Decision trees

Pharmacoepidemiology

BACKGROUND

A significant proportion of patients is reported to suffer from drug-related morbidity (DRM), such as adverse drug reactions (ADRs) and therapeutic failure [1,2], but evidence from observational studies and modelling studies are partially inconsistent. In an American modelling study using probability estimates of an expert panel of pharmacists in the 1995, 40% of ambulatory patients receiving medication was estimated to experience DRM [3]. According to Swedish pharmacists' recent estimation, 61% of all patients utilising healthcare experience DRM [4]. These estimates on the proportion of patients with DRM are higher than in most observational studies, in which the median frequency of adverse drug events (ADEs) among inpatients is reported to be 6% [2], and 5% of hospital admission is estimated to be drug-related, with a range from 0.01% to 54% in individual studies [1]. In the modelling studies with a pharmacist expert panel, pharmacists' perception on DRM may be subjective and estimates on DRM could differ, if other health professionals were used as experts, as suggested by a modelling study in nursing homes [5].

In modelling studies with a pharmacist-panel, the costs to healthcare due to DRM are extensive, in Sweden EUR 6.6 billion among all patients in 2010 [4], and in the United States USD 89 billion among ambulatory patients in 1995 [3] and USD 117 billion in 2001 [6]. However, patient-level costs were EUR 1645 per *patient with DRM* in the Swedish modelling study [4], which is lower than in most observational studies [7]. As modelling studies' cost estimates are based on pharmacists' perceptions on the clinical outcomes of DRM, in addition to their high estimates on the proportion of patients with DRM, the costs of DRM may also differ if a panel of other health professionals was used in modelling studies.

For preventing unnecessary patient harm and costs for healthcare, the preventability of DRM is particularly interesting. The Swedish modelling study's estimate that 45% of *all patients with DRM* suffer from preventable DRM [4] was similar to or slightly higher than in observational studies [2,8-13]. However, the Swedish modelling study's conclusion [4] that 27% of *all patients* experienced preventable DRM was significantly higher than in observational studies [10,11,13].

Modelling studies using experts' opinion for probabilities of DRM and related outcomes may provide valuable evidence on DRM in a population level, as observational studies are limited to specific sub-population, such as patients of certain care units. However, the results of previous modelling studies using pharmacists' probability estimates, based on their subjective view and experience in clinical practice, are partially inconsistent with other evidence. Thus, other health professionals' estimates should be used in modelling studies to investigate whether results vary. The purpose of this modelling study was to estimate the proportion of patients with DRM and preventable DRM and to estimate the cost-of-illness (COI) of DRM in Sweden based on *physicians'* expert opinion.

METHODS

A conceptual model on DRM with a decision tree was modified from a previous American study [3]. The model was modified for the Swedish health system and for an expert panel of physicians (Fig. 1). The panel estimated probabilities of DRM and related outcomes in the decision tree, using modified Delphi methodology with two rounds [14]. Physicians working in outpatient care (n=11) provided estimates for outpatients, and physicians working with inpatients (n=8) for inpatients. However, DRM among inpatients could also originate from outpatient settings. To gain approximately 20 panellists representing both outpatient and inpatient care and different specialties, a strategic stratified sample of 20 physicians active in Drug and Therapeutics Committees was invited to participate in the study. Six strata represented specialties or combinations of specialties, and the desired number of participants in each stratum was chosen in proportion of patient consultations in each stratum. The invited physicians were also chosen to represent rural and urban as well as academic and non-academic healthcare. When an invited physician in a stratum declined participation, another physician in the stratum was invited to replace the physician, based on a pre-defined list of potential participants representing different specialties. From a total of 53 invited physicians, 19 specialist physicians representing the six strata consented, forming the expert panel. Five were specialised in general medicine, four in internal medicine, and three in geriatrics. Each of the remaining seven was specialised either in psychiatry, dermatology, rheumatology, urology, infections diseases, general surgery or paediatrics. Six of the physicians practiced in university hospitals and eight in general hospitals. Eight of the physicians based in a hospital practiced primarily with inpatients and six with outpatients. Five physicians practiced in primary care in district healthcare centres. Twelve physicians were male and seven female, with a mean age of 57 years (range 45-69).

In section A of the decision tree, physicians estimated the probabilities of outcomes of drug therapy among their patients (Fig. 1). New medical problems (NMPs), therapeutic failure (TF) and a combination of NMPs and TF as outcomes represented DRM. DRM could originate from prescribed drugs, non-prescribed drugs or complementary medicines, but morbidity related to drugs without approval for medical purposes was excluded. NMPs included ADRs, drug dependence and intoxications by overdose. TF included insufficient effects of medicines due to erroneous therapy, including morbidity due to lack of drug therapy despite indication,

or when rational use of medicines was insufficient. In section B, physicians estimated the proportion of patients with preventable DRM according to established criteria, including DRM that was “*due to a drug treatment procedure inconsistent with present day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account*” or DRM when “*the prescription was not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands*” [15]. The clinical outcomes of DRM were estimated in section C. In sections A and C, the response alternatives were mutually exclusive. In section C, respondents were instructed to choose the worst response alternative when multiple clinical outcomes due to DRM were present. The conceptual model was the same for outpatients and inpatients apart from one response alternative in section C (Fig. 1), where the probability of a hospitalisation was estimated for outpatients and the probability of prolonged hospital stay for inpatients. The Swedish conceptual model was piloted with six pharmacists, six physicians and four nurses, representing both outpatient and inpatient care. Based on the pilots, the arms of the decision tree were adapted for a panel of outpatient and inpatient physicians (Fig. 1) and the face and content validity of the final model was assessed.

In the first round, at least one researcher (DA, HG or KH) instructed the physicians face-to-face in interpreting the decision tree. The physicians provided their estimates independently, in writing, and were encouraged to leave written comments. Additional information was collected on the participants’ age, sex and workplace. The participants also completed an appraisal of the decision tree, in which they estimated in a five-point Likert scale how easy each section of the decision tree was to answer. In the second round, conducted through mail, participants could adjust their estimates after receiving interquartile ranges of the entire panel’s estimates and a copy of their own estimates from the first round. The appraisal of the decision tree could also be revised. As one physician made no revisions in section A, four in section B, one in section C, and five in the appraisal, answers from the first round were used for these questions. Answers were returned in a pre-paid envelope.

Analyses

Proportion of patients with DRM and preventable DRM

The estimates were analysed separately for outpatients and inpatients. The proportion of patients with DRM was calculated using mean probabilities for patients experiencing NMPs and TF.

The proportion of preventable DRM (NMPs or TF) *among patients with DRM* was calculated by taking respondents' mean estimates. The total proportion of patients with preventable DRM *among patients with DRM* was calculated by weighting, for each respondent, the proportion of patients with preventable NMPs and TF (among patients with NMPs and TF) by the mean proportion of NMP and TF patients among *all DRM patients* (i.e. patients with any NMPs or TF). The weighted estimates were summed for each respondent and a mean was taken.

The proportion of patients with preventable NMPs and TF *among all patients* was calculated by weighting, for each respondent, the proportion of patients with preventable NMPs and TF (among patients with DRM) by the estimated probabilities of NMPs and TF *among all patients*. The mean of the sum of these estimates represented the total proportion of patients with preventable DRM.

Even though the types of distributions of the responses were not apparent due to the small sample size, the distributions were reasonably symmetrical. Therefore and because means and medians did not differ notably, the use of means was considered appropriate. Calculations were done using STATA version 10.0.

Cost-of-illness analyses

The COI analysis was conducted separately for DRM among outpatients and inpatients, folding back in the decision tree (TreeAge Pro Excel 2009). Firstly, conditional probabilities for clinical outcomes were calculated by multiplying mean probabilities for each type of DRM with mean probabilities for clinical outcomes of each type of DRM. Secondly, each conditional probability was multiplied by its pathway costs (Table 1), resulting in cost estimates for each clinical outcome. The sum of these clinical outcome costs represented the total COI of DRM, per outpatient and inpatient. The annual COI of DRM among outpatients and inpatients was calculated under the assumption that 70% of residents in Sweden visit outpatient care and 9.5% of residents are hospitalised, at least once annually [16,17].

The pathway costs used in the main analyses and the minimum and maximum pathway costs for each clinical outcome were determined from their cost-generating components (Table 1). The minimum pathway costs represented the most conservative cost estimate and the maximum pathway costs a reasonable worst-case scenario. The cost-generating components were decided based on published literature [8,18-21], and the researchers' conservative estimates. Monetary values for the components were determined from national statistics [22-24] and personal communications with register holders [Gyllenstein H. Personal communication] on costs of healthcare and drug utilisation. The cost-generating components and pathway costs were the same for outpatients and inpatients apart from *no additional treatment*, *additional treatment* and *specialist referral*. For outpatients, the costs of these clinical outcomes included an initial contact to primary care, while contact to primary care was omitted from costs for inpatients. Swedish crowns were converted to Euro (EUR) using the 2010 exchange rate [25].

Sensitivity analyses of cost-of-illness

To investigate the robustness of the COI analysis, the probabilities of DRM and its clinical outcomes were varied from the first to the third quartile of the participants' estimates. In another sensitivity analysis, clinical outcomes with most insecurity in the COI analysis were investigated through Tornado diagrams, in which the determined cost-generating components and pathway costs for each clinical outcome are varied from minimum to maximum costs (TreeAge Pro Excel 2009).

RESULTS

Proportion of patients with DRM and preventable DRM

Physicians estimated that $51\pm 22\%$ (mean $\pm$ standard deviation) of all outpatients and $54\pm 17\%$ of all inpatients experience DRM (Table 2). Among outpatients with DRM, $24\pm 11\%$ was estimated to experience preventable DRM. Among inpatients with DRM, DRM was considered preventable for $31\pm 15\%$. $12\pm 8\%$ of all outpatients and $16\pm 7\%$ of all inpatients were estimated to experience preventable DRM. The proportions of patients with all and preventable NMPs, TF and their combinations are presented in Table 2.

Cost-of-illness of DRM

Physicians estimated that 26% of outpatients with NMPs, 14% with TF and 8% with the combination of both require *no addition treatment* due to DRM (Table 3). Of inpatients, 27% with NMPs, 7% with TF and 7% with their combinations was estimated to require *no additional treatment*. For the remaining proportions of outpatients and inpatients with DRM, the DRM was estimated to result in *additional treatment, specialist referral, prolonged hospital stay, hospitalisation, advanced specialist care or death*. Based on the probability estimates for these clinical outcomes, the COI was EUR 376 per *outpatient* and EUR 838 per *inpatient* (Table 4). Of the COI per outpatient, *hospitalisations* and *advanced specialist care* due to DRM caused 75% (283 EUR) of the costs. *Prolonged hospital stay* and *advanced specialist care* due to DRM caused 81% (678 EUR) of the costs among inpatients. The COI of DRM per outpatient and inpatient correspond to EUR 730 per *outpatient with DRM* and EUR 1542 per *inpatient with DRM*. When investigating the types of DRM, the COI of NMPs was EUR 751 per *outpatient experiencing NMPs exclusively* and EUR 1036 per *inpatient experiencing NMPs exclusively*. The COI of TF was EUR 600 per *outpatient experiencing TF exclusively* and EUR 1094 per *inpatient experiencing TF exclusively*. The COI of combinations of NMPs and TF was EUR 887 among outpatients *experiencing both NMPs and TF* and EUR 3252 among inpatients *experiencing both NMPs and TF*. Extrapolated to the Swedish population, the total annual COI of DRM was EUR 2.5 billion for outpatients and EUR 0.8 billion for inpatients.

Sensitivity analyses of cost-of-illness

The COI of DRM per *outpatient* ranged from EUR 97 for the first quartile to EUR 447 for the third quartile probability estimates. The range was EUR 209-1177 for *inpatients*. Of the clinical outcomes of DRM among outpatients, the costs differed the most for *hospitalisation* (cost range EUR 63-257), when the first and third quartile probability estimates were used. Among inpatients, the cost difference was the largest for *advanced specialist care* (cost range EUR 87-677). According to the Tornado diagrams, the COI among outpatients was the most sensitive to changes in costs resulting from *hospitalisations*, with cost estimates of EUR 330 per outpatient using minimum and EUR 445 using maximum pathway costs (Fig. 2 and 3). The COI among inpatients was the most sensitive to costs resulting from *prolonged hospital stay* (cost range EUR 509-1037).

DISCUSSION

In our modelling study, Swedish physicians perceived that approximately half of their patients experience DRM. The estimates were almost equal for outpatients and inpatients. Our estimates were lower than Swedish pharmacists' estimation that 61% of all patients attending health care experience DRM [4], but higher than American pharmacists' estimate in 1995 that 40% of outpatients who receive medicines suffer from DRM [3]. Comparing the Swedish studies, pharmacists working clinically may have estimated the proportion of DRM higher, if they encounter patients with DRM in their clinical practice, rather than average patients. Alternatively, pharmacists working in the community may encounter persons with DRM who do not visit outpatient physicians. Pharmacists may also provide high DRM estimates, perhaps unconsciously, to justify their professional role. Physicians may have given lower estimates because they were asked to provide estimates from their own experience and may have perceived that acknowledging DRM would reflect poorly on their own practice. Nonetheless, the modelling studies combined suggest that up to 40-60% of all patients may experience DRM, even though results from modelling studies must be compared and interpreted with caution.

In our and previous modelling studies using health professionals' expert opinion [3,4], the proportion of patients with DRM is significantly higher than in reviews of observational studies [1,2], in which approximately 5-6% of patients attending hospitals is estimated to experience DRM. As observational studies among outpatients commonly investigate drug-related hospital admissions, estimates based on experts' opinions may be higher because they include DRM in primary care that does not lead to hospitalisations. For both inpatients and outpatients, part of DRM may be overseen in observational studies, because different data sources, such as self-reports and medical records, detect different types of DRM and none of them alone detects all DRM [26]. In addition, modelling studies' estimates may be higher due to a broader definition for DRM. TF is often unspecified in observational studies, potentially leading to overlooking it. When patients with TF exclusively are excluded from our results, physicians' estimates were 36% of outpatients and 34% of inpatients, still significantly higher than in observational studies. Finally, estimates on DRM in modelling studies using an expert panel may be high, because informants were active in Drug and Therapeutics Committees, and thus had an interest in drug safety. However, as physicians' estimates on DRM were also

higher than in observational studies, high estimates based on pharmacists' expert opinion are not entirely explained by pharmacists' subjective view. Thus, DRM in the entire healthcare may be more common than observational studies suggest.

Based on Swedish physicians' estimates, the direct costs of DRM were EUR 376 per *outpatient* and EUR 838 per *inpatient attending healthcare*. Although differing methods for modelling DRM in different health systems hinders the direct comparison of the resulting costs, our estimate for outpatients is similar to American pharmacists' estimates that in the United States DRM cost USD 194 per *physician outpatient visit* in 1995 [3], and 376 USD in 2001 [6]. Our cost estimate for outpatients is also similar to cost estimates in Germany, where DRM was estimated to cost EUR 434 per *outpatient visit*, combining American probability estimates and German data on clinical outcomes [27]. However, Swedish pharmacists estimated DRM to cost markedly more, EUR 997 per *patient attending healthcare* [4]. The difference between Swedish pharmacists' and physicians' cost estimations is partially attributable to physicians' lower estimates for the proportion of patients with DRM. Moreover, the pharmacists' estimates were based on all patients attending healthcare, while physicians responded based on patients either in outpatient or inpatient settings. Thus, physicians' estimates did not represent DRM in all patients attending healthcare. For outpatients, the difference is largely explained by physicians' more conservative probability estimates for the most severe and expensive clinical outcomes. According to physicians, DRM leads to a hospitalisation among 5% of outpatients with DRM, to advanced specialist care among 0-2% and to death among 0%. According to pharmacists, DRM causes a hospitalisation to 9-15% of all patients with DRM, advanced specialist care to 2-4% and death to 1-4% [4]. As for the probability of DRM, the estimate differences may arise from different professional roles. Due to physicians' lower cost estimates per patient, the extrapolated annual costs of the DRM for Swedish healthcare, EUR 2.5 billion for outpatients and EUR 0.8 billion for inpatients, are also lower than estimated by pharmacists [4], EUR 6.6 billion in total for all patients. Even though physicians' costs estimates were lower than pharmacists', the annual costs of DRM for the Swedish healthcare were also substantial according to physicians.

Compared to observational studies' results [7], our cost estimates per *patient with DRM* are low, as in other modelling studies [4,27]. In observational studies, the cost of DRM has been USD 422-7062 per *outpatient with DRM* and USD 2284-5640 per *inpatient with DRM* (2000

values) [7]. Based on physicians' estimates in our study, DRM costs EUR 730 per *outpatient with DRM* and EUR 1542 per *inpatient with DRM*, while Swedish pharmacists estimated that DRM costs EUR 1645 per *patient with DRM* [4]. In Germany, the average cost per *outpatient with DRM* was EUR 381 [27]. For both outpatients and inpatients, observational studies' average per patient costs were probably higher because they commonly focus on costs of emergency visits, hospitalisations and prolonged hospital stay. In modelling studies, the costs included also relatively inexpensive clinical outcomes, such as *no additional treatment* and *additional treatment*, which decreases the average costs.

Swedish physicians' estimates on the proportion of patients with preventable DRM were lower than estimates by pharmacists [4,28]. *Among patients with DRM*, 24% of outpatients and 31% of inpatients were perceived to experience preventable DRM by the physicians, while Swedish pharmacists estimated that *among patients with DRM*, 45% suffer from preventable DRM [4]. Although the proportion of preventable DRM was not assessed in the American modelling study, American pharmacists estimated that 53-60% of NMPs and TF could be avoided if ambulatory patients received pharmaceutical care [28]. Pharmacists' avoidability estimates were higher than physicians' also in another American modelling study on DRM in nursing homes [5], in which pharmacists estimated that 48% and physicians that 34% of DRM is avoided through pharmaceutical care, although no statistical significance between the professionals' estimates was observed. In literature reviews of observational studies, the median or pooled preventability of drug-related admissions, ADEs or ADRs has been between 21% and 59%, with a range of 11-90% in individual studies [2,8-13]. Pharmacists' preventability estimates were slightly higher and physicians' slightly lower than in most observational studies. The reasons for pharmacists' high and physicians' low estimates may be the same as for the occurrence of DRM. Preventability was also defined through the presence of sub-standard care in our study [15], which may have discouraged physicians to acknowledge preventability. As methods for assessing the preventability of DRM are limited and diverse [29,30], the preventability of DRM and the proportion of patients with preventable DRM remains unknown, but appears to range between 20-60%.

Swedish physicians' estimates that 12% of *all outpatients* and 16% of *all inpatients* experience preventable DRM were lower than Swedish pharmacists' estimate, 27% for all patients [4]. As discussed before, the difference is partially attributable to physicians' lower

estimates for the proportion of patients with DRM, but mainly to physicians' lower preventability estimates. However, both expert panels' estimates are markedly higher than in observational studies, in which the median or pooled proportions of patients with preventable DRM have been between 2% and 4% [10,11,13]. This difference originates from the expert panels' higher estimates on the proportion of all patients with DRM, while preventability estimates were similar. As for the proportion of patients with all DRM, these results suggest that also preventable DRM in the entire healthcare may be more common than observational studies have reported.

Several limitations arise from using a decision tree. The decision tree was a simplified model of DRM and thus, does not represent all scenarios for and outcomes of DRM. In our pilot study, informants perceived long-term consequences of DRM, such as residential care, impossible to estimate. We therefore excluded long-term consequences from the decision tree, which may have lead to underestimating the costs of DRM. As decision trees lack a time window [31], we were unable to determine the prevalence of DRM in a given time which limits the extrapolation of our results. Informants may also have considered lifetime prevalence, resulting in high estimates for patients experiencing DRM. However, we believe this is unlikely, because the physician were asked the proportion of patients that *have* various outcomes, opposite to *have had* which would refer to life time prevalence. In addition, we instructed our panellists to provide estimates based on their current experience.

As an expert panel and a modified Delphi technique were used for gaining probabilities in the decision tree, our estimates represent the physician panellists' perception and have to be interpreted with caution. Even though using empirical probability estimates in modelling studies is recommended, the Delphi technique is appropriate when no empirical data is available [32], which was the case for the proportion of patients with DRM and preventable and the clinical outcomes of DRM in the entire healthcare. Traditionally in the Delphi methodology, multiple rounds are performed until a consensus within the panel is reached. We decided in advance to conduct two rounds. Although mean estimates did not differ between the rounds, standard deviations narrowed slightly after the second round, though were still large. A better consensus may have been reached if further rounds had been performed. Further, the composition of the panel may have influenced the results, including the physicians' medical specialties, practice settings and previous experience.

As definitions for DRM and criteria for preventability are diverse [30,33,34], our estimates may not be comparable to studies using other definitions and criteria. Unlike in the American modelling study [3], DRM could in our study originate from non-prescribed drugs or complementary medicines and TF could be caused by lack of drug therapy despite indication. Thus, we included DRM among all patients attending outpatient or inpatient care, rather than the number of visits resulting in prescribed drugs. Our informants may also have interpreted the definitions differently, causing variation in their estimates. To facilitate an accurate interpretation of the decision tree and the definitions, we purposefully selected physicians active in Drug and Therapeutics Committees. Further, we explained the decision tree and the definitions to each physician face-to-face before they provided probability estimates. Despite our efforts to facilitate the interpretation of the model, nine (47%) physicians perceived section A, 12 (63%) section B and 13 (68%) section C of the decision tree as *somewhat difficult* or *difficult* (score 4 or 5 in a five-point Likert scale) to answer after the second round, which must be considered when their mean estimates are interpreted.

The COI of DRM was sensitive to changes in physicians' probability estimates for the proportion of patients with DMR and clinical outcomes of DRM, with almost five-fold cost increase from the most conservative probabilities to the least conservative. In addition, the COI analysis was sensitive to changes in the pre-determined pathway costs for clinical outcomes, with variations in pathway costs of hospitalisation and prolonged hospital stay influencing the COI analyses the most. Thus, the COI of DRM among outpatients and inpatients in our study are approximates and need to be verified in empirical studies. Since indirect costs were excluded, our cost estimations may be underestimations of the economic burden of DRM to the society.

CONCLUSIONS

Swedish physicians estimated that every other outpatient and inpatient experiences DRM, which is often preventable and costly. These estimates were lower than Swedish pharmacists', indicating that informants' profession influences the results in modelling studies using experts' estimates. Physicians' estimates on the proportion of patients with DRM in the entire healthcare were still higher than in observational studies in restricted sub-populations. Thus,

both non-preventable and preventable DRM may be more common in the general population than the current evidence suggests. To examine the findings of modelling studies, future empirical research should investigate DRM and its characteristics in the general population.

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CONFLICTS OF INTEREST

The authors' work was independent of the sponsor, The National Corporation of Swedish Pharmacies (Apoteket AB), who had no role in the study design, data collection, analysis and interpretation, writing the manuscript, or in the decision to submit the manuscript for publication. The authors declare that they have no conflicts of interest.

DISCLAIMER

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Medical Product Agency.

Fig. 1 Layout and response alternatives in the conceptual model on drug-related morbidity

¹Physicians working in outpatient care (n=11) provided estimates for outpatients

²Physicians working with inpatients (n=8) provided estimates for inpatients

³Patients with new medical problem, therapeutic failure or their combinations represent patients with drug-related morbidity

Fig. 2 Tornado diagram sensitivity analysis for the cost-of-illness of drug-related morbidity (DRM) among outpatients. The expected value in is the resulting costs from varying the pathway costs of each clinical outcome from minimum (min) to maximum (max) costs in euro (EUR)

Fig. 3 Tornado diagram sensitivity analysis for the cost-of-illness of drug-related morbidity (DRM) among inpatients. The expected value in is the resulting costs from varying the pathway costs of each clinical outcome from minimum (min) to maximum (max) costs in euro (EUR)

Table 1 Cost-generating components and pathway costs of clinical outcomes resulting from drug-related morbidity, used in the main analysis and the Tornado diagram sensitivity analysis

Clinical outcome	Main analysis		Minimum estimation		Maximum estimation	
	Cost-generating components	Pathway cost (EUR)	Cost-generating components	Pathway cost (EUR)	Cost-generating components	Pathway cost (EUR)
No additional treatment	<i>Outpatients:</i> 1 telephone call to physician ^a <i>Inpatients:</i> no additional healthcare contact	<i>Outpatients:</i> 44 <i>Inpatients:</i> 0	No additional healthcare contact	0	1 physician visit ^a	131
Additional treatment	<i>Outpatients:</i> 1 physician visit ^a + 1 additional prescribed drug ^b <i>Inpatients:</i> 1 nurse consultation ^a + 1 additional prescribed drug ^b	<i>Outpatients:</i> 151 <i>Inpatients:</i> 65	<i>Outpatients:</i> 1 nurse visit ^a <i>Inpatients:</i> No additional healthcare contact	<i>Outpatients:</i> 45 <i>Inpatients:</i> 0	2 physician visits ^a	262
Specialist referral	<i>Outpatients:</i> 1 physician visit ^a + 1 specialist physician visit ^a <i>Inpatients:</i> 1 specialist physician consultation ^a	<i>Outpatients:</i> 427 <i>Inpatients:</i> 296	<i>Outpatients:</i> 1 telephone call to physician ^a + 1 specialist physician visit ^a <i>Inpatients:</i> 1 nurse consultation ^a	<i>Outpatients:</i> 340 <i>Inpatients:</i> 45	<i>Outpatients:</i> 1 physician visit ^a + 2 specialist physician visit ^a <i>Inpatients:</i> 2 specialist physician consultations ^a	<i>Outpatients:</i> 723 <i>Inpatients:</i> 592
Prolonged hospital stay	2 additional days in hospital [18,19] ^c	1850	1 additional day in hospital ^c	925	9 additional days in hospital [20] ^c	8324
Hospitalisation	9 days in hospital [8] ^c	8324	7 days in hospital [8] ^c	6474	12 days in hospital [8] ^c	11099
Advanced specialist care	9 days in hospital ^c + 2 days in intensive care [21] ^d	13893	2 days in hospital ^c + 1 day in intensive care ^d	4634	9 days in hospital ^c + 4 days in intensive care ^d	19461
Death	9 days in hospital ^c	8324	2 physician consultations ^a	262	9 days in hospital ^c + 2 days in intensive care ^d	13893

EUR Euro

^aAverage cost of a physician (EUR 131), nurse (EUR 45) or specialist physician (EUR 296) consultation in somatic healthcare in Sweden during 2010, and telephone calls are weighted as one third of the cost of a visit [23]

^bAverage benefit (EUR 20) of a dispensed prescription drug in Sweden during 2010 [Gyllensten H. Personal communication]

^cAverage daily hospital cost in somatic healthcare in Sweden during 2009 (EUR 909) [22], adjusted to 2010 value using a Swedish healthcare inflation index (price index with

quality-adjusted wages for the county, including medicines 1.7%) [24]

^dAverage daily cost in an intensive care in Sweden during 2009 (EUR 2738), estimated using the assumption that personnel costs are 70% of the total costs [Gyllensten H. Personal communication], adjusted to 2010 value using a Swedish healthcare inflation index (price index with quality-adjusted wages for the county, including medicines 1.7%) [24]

Table 2 Mean proportions of outpatients and inpatients with DRM and preventable DRM estimated by physicians (n=19), by type of DRM

Type of DRM	Proportion of patients with DRM among all patients % (SD)		Proportion of patients with preventable DRM among patients with DRM % (SD)	
	Outpatients	Inpatients	Outpatients	Inpatients
New medical problem	26 (15)	22 (10)	21 ^b (13)	43 ^b (13)
Therapeutic failure	16 (7)	21 (6)	29 ^c (19)	29 ^c (15)
New medical problem + therapeutic failure	10 (8)	12 (8)	20 ^d (15)	25 ^d (13)
TOTAL	51 ^a (22)	54 ^a (17)	24 ^e (11)	31 ^e (15)

DRM drug-related morbidity

SD standard deviation

^aCalculated by summing the proportions of DRM types. Because of rounding, the sum may not equal to the total %

^bAmong patients with new medical problems exclusively

^cAmong patients with therapeutic failure exclusively

^dAmong patients with a combination of new medical problems and therapeutic failure

^eCalculated by weighting the proportion of patients with preventable new medical problems and therapeutic failure (among patients with new medical problems and therapeutic failure) by the proportion of patients with new medical problems and therapeutic failure among all DRM patients

Table 3 Mean and conditional probabilities of clinical outcomes due to drug-related morbidity estimated by physicians (n=19), separately among outpatients and inpatients

Clinical outcomes of DRM ^a	Mean probabilities		Conditional probabilities ^b	
	Outpatients %	Inpatients %	Outpatients %	Inpatients %
New medical problems^a				
No additional treatment	26	27	7	6
Additional treatment	55	36	14	8
Specialist referral	12	13	3	3
Prolonged hospital stay	-	18	-	4
Hospitalisation	5	-	1	-
Advanced specialist care	1	3	0	1
Death	0	3	0	1
Therapeutic failure^a				
No additional treatment	14	7	2	2
Additional treatment	70	46	11	10
Specialist referral	11	20	2	4
Prolonged hospital stay	-	21	-	4
Hospitalisation	5	-	1	-
Advanced specialist care	0	3	0	1
Death	0	2	0	0
New medical problems and therapeutic failure^a				
No additional treatment	8	7	1	1
Additional treatment	68	35	7	4
Specialist referral	17	23	2	3
Prolonged hospital stay	-	13	-	2
Hospitalisation	5	-	0	-
Advanced specialist care	2	19	0	2
Death	0	3	0	0

DRM drug-related morbidity

^aNew medical problems, therapeutic failure and their combinations represent drug-related morbidity

^bConditional probability is the proportion of all patients experiencing a specific clinical outcome due to new medical problems or therapeutic failure, and is calculated by multiplying probabilities of new medical problems and therapeutic failure by the probabilities of their clinical outcomes

Table 4 Cost-of-illness of drug-related morbidity per outpatient and inpatient, separately for each clinical outcome

Clinical outcomes of DRM^a	Cost-of-illness per outpatient (EUR)	Cost-of-illness per inpatient (EUR)
New medical problems^a		
No additional treatment	3	0
Additional treatment	22	5
Specialist referral	14	8
Prolonged hospital stay	-	74
Hospitalisation	107	-
Advanced specialist care	40	91
Death	8	48
Therapeutic failure^a		
No additional treatment	1	0
Additional treatment	17	6
Specialist referral	8	12
Prolonged hospital stay		81
Hospitalisation	61	-
Advanced specialist care	8	86
Death	1	41
New medical problems and therapeutic failure^a		
No additional treatment	0	0
Additional treatment	10	3
Specialist referral	7	8
Prolonged hospital stay	-	28
Hospitalisation	39	-
Advanced specialist care	28	318
Death	2	30
Total cost-of-illness	376^b	838^b

DRM drug-related morbidity

EUR Euro

^aNew medical problems, therapeutic failure and their combinations represent drug-related morbidity

^bThe same as by folding back of the decision tree, the total cost-of-illness may not total the sum of the costs of clinical outcomes because of rounding

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