A Cost-Utility Analysis of Phosphodiesterase Type 5 Inhibitors in the Treatment of Erectile Dysfunction

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Highlights

- Only a few cost-effectiveness analyses were identified for erectile dysfunction treatments. To the best of our knowledge, this is the first cost-utility analysis simultaneously comparing three separate PDE5 inhibitors.
- No other cost-utility analyses were identified that also explore the cost-effectiveness of treating erectile dysfunction in a diabetic population.
- The cost-utility model created for this paper may be used to aid decision makers under conditions of uncertainty in making informed decisions related to PDE5 inhibitor treatment of erectile dysfunction.

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to obtain or maintain a penile erection sufficient for satisfactory sexual performance [1]. ED is a debilitating condition that may profoundly impact the sexual health and quality of life (QoL) for the men affected, as well as those of their sexual partners [2]. The diagnosis of ED involves a clinical evaluation, most often done by a general practitioner (GP). A study conducted in 2001 assessed the prevalence of ED in Norwegian males over 40 years of age [3]. The results indicated that nearly 60% of men older than 40 years have some degree of ED. If we exclude those with mild ED and include only those with moderate to severe ED, this number is reduced to 32% [4].

Since the introduction of sildenafil (the active ingredient in Viagra) in 1998, oral phosphodiesterase type 5 (PDE5) inhibitors quickly became the first-line treatment for men with ED. Today, in addition to sildenafil, the most commonly-used oral PDE5 inhibitors in Norway are tadalafil and vardenafil. A large number of clinical studies have been conducted since the introduction of sildenafil, demonstrating that PDE5 inhibitors are highly effective and well-tolerated for treating men with ED [5-7]. Efficacy in ED treatment is defined as attaining an erection sufficient for sexual performance, also referred to as treatment response [8]. PDE5 inhibitors should be administered in on-demand doses, and these doses should be adjusted according to the patient's efficacy and tolerability outcomes. Adverse events (AEs) associated with PDE5 inhibitor treatment are generally mild in nature and self-limited through continuous use [9, 10]. Full details on side effects are described in detail in the summary of product characteristics (SPCs) issued by the European Medicines Agency (EMA)[11-13].

PDE5 inhibitor treatment of ED has not been traditionally considered for reimbursement in Norway, due to legislation prohibiting reimbursement for ED medicines. However, this was changed in 2015, allowing for holders of the Marketing Approvals of ED medicines to apply for reimbursement. Still, reimbursement applications have been postponed, partly because of a lack of knowledge on the cost-effectiveness of treatment, and partly because of budgetary consequences of granting reimbursement [14]. Despite the fact that PDE5 inhibitors have been on the market for almost 20 years, literature regarding the cost-effectiveness of PDE5 inhibitors is scarce [15-17]. Moreover, no cost-effectiveness analysis has been identified that simultaneously compares three separate PDE5 inhibitors.

The main objective of this paper was to assess from a healthcare perspective the cost-effectiveness of three separate PDE5 inhibitors in erectile dysfunction treatment, compared to "no treatment". This study intends to aid decision makers under conditions of uncertainty in making informed decisions concerning reimbursement of PDE5 inhibitor treatment. The cost-effectiveness model described in this paper could be utilized in other countries and settings to assess the cost-effectiveness of PDE5 inhibitors of interest.

METHODS

Patient population

The primary patient group analyzed was 55-year-old men suffering from ED with no specific precondition (hereafter referred to as "primary patient population"). This patient group was established to capture the aspect of treating the general ED population using PDE5 inhibitors.

The secondary patient group analyzed was men with ED suffering from diabetes (hereafter referred to as "secondary patient population"). This patient group was established to capture the aspect of treating ED in a population with a serious comorbidity, as the prevalence of ED is substantial among the diabetic population [18].

Intervention

The analysis included three PDE5 inhibitor treatment options, in addition to a no-treatment option. The PDE5 inhibitor treatment options comprised sildenafil (50mg and 100mg), tadalafil (10mg and 20 mg), and vardenafil (10mg).

Description of the model

A Markov model was developed to estimate long-term treatment costs and health-related quality of life (HRQoL) for men with ED [19]. Figure 1 illustrates the state-transition Markov model. In order to capture all the important cost consequences and health outcomes of the three PDE5 inhibitor treatments compared to "no treatment", a 10-year time horizon was chosen. As the treatment with PDE-5 inhibitors is usually not associated with long-term health outcomes, a further increased model time horizon would most likely only increase the model uncertainty. Furthermore, a shorter time horizon, although probably a viable option, could misrepresent some of the short duration model features. The structure of the model was designed to reflect the complexities of health states and treatment options of ED, based on treatment protocols and relevant literature. Each cycle length was one month,

and the individual could only be in one health state per cycle.

In Model A, we simulated the PDE5 inhibitor treatments, including six health states that capture efficacy and harms: insufficient response (ED), insufficient response with treatment-related adverse events (ED with AE), sufficient response (No ED), sufficient response with treatment-related adverse events (No ED with AE), ending PDE5 inhibitor treatment (Dropout), and dying (Death). The cohort were assigned equally to either "no treatment" or one of the three mutually-exclusive treatment options ("sildenafil 50 mg", "tadalafil 10 mg", or "vardenafil 10 mg"). All individuals started in the health state "ED"; the patient would stay in "ED" if he had an insufficient response or would move to one of the other five health states ("ED with AE", "No ED", "No ED with AE", "Dropout", and "Death"). The transition between health states were treatment-dependent, and for adverse events the probabilities also depended on the dose.

Model B represents the follow-up of AEs that individuals experienced during treatment (for health state "ED with AE" and "No ED with AE" in Model A). The probabilities for each of the AEs were determined by the treatment option and the medication strength.

Model C was constructed to simulate the switches between PDE5 inhibitor treatments and between medication dose. Based on the efficacy and harm outcomes of each PDE5 inhibitor treatment, Model C involved 5 mutually-exclusive treatment strategies, each assigned with an identical model A and B structure, but with different transition probabilities and costs.

Individual subjects could switch from one of the three treatment options to another at any given time (represented by model C) if they experienced insufficient treatment response or any treatment-related AE (represented by the health states "ED", "ED with AE", and "No ED with AE"). During the first two months of treatment, the individuals using either sildenafil or tadalafil went through a 'dose optimization period', where they had the possibility to double their starting dose in the case of insufficient effect. It was assumed that patients would only increase their treatment dose if experiencing insufficient effect from their current treatment dose (i.e. in the "ED" and "ED with AE" health states). This transition was illustrated in Model C. After the two-month dose optimization period, the individuals could stay on their current dose, switch to another PDE5 inhibitor, or stop using PDE5 inhibitors all together (represented as "Dropout"). In the case of switching to another PDE5 inhibitor, the patients

had a new two months dose optimization period for the new PDE5 inhibitor treatment.

In Appendix A1 (Figure A1), an alternative illustration of Model A and C is presented. Arrows represents possible transitions between health states. As an example, the probability of switching treatment could occur at any time during the model time horizon, as long as the individual was in a health state with ED (indicating insufficient treatment response) or AEs. These health states are illustrated within the dashed squares in Figure A1.

All individuals, regardless of current state, had an equal chance of death at any given cycle.

[Figure 1]

Health outcomes

The primary health outcome was quality-adjusted life-years (QALYs) [20]. The QALY combines length of life with health-related quality of life (HRQoL) into a single generic measure, allowing for comparison both within and across various treatment options.

The HRQoL is the value assigned to a particular health state and is intended to reflect physical, psychological, and social well-being. HRQoL uses a numerical expression, normally between 1 (perfect health) and 0 (dead) [21].

Costs

A societal perspective was applied when estimating costs associated with ED treatment. Costs directly and indirectly associated with PDE5 inhibitor treatment were included. The direct costs of ED treatment included the cost of medication and visits to the general practitioner (GP); the indirect costs included patient transportation.

All costs were half-cycle corrected [22]. A discount rate of 4% per year were used for future costs, as recommended by the Norwegian Ministry of Finance and by the Norwegian Medicines Agency (NoMA) [23]. All costs were adjusted to the year 2017.

Cost-utility analyses

We performed a cost-utility analysis (CUA) in which the results were reported as the incremental cost-

effectiveness ratios (ICER), defined by the incremental cost per unit of effectiveness (QALYs). For example, the ICER of sildenafil treatment compared to the "no-treatment" option was defined as:

$$ICER_{sild,notr.} = \frac{Cost_{sildenafil} - Cost_{No\ treatment}}{QALY_{sildenafil} - QALY_{No\ treatment}} = \frac{\Delta C}{\Delta E} = \frac{Incremental\ cost}{Incremental\ effect}$$

In the case of a negative ICER, the evaluated PDE5 inhibitor is either dominant (more effective and less costly) or dominated (less effective and more costly) [24]. For a given willingness-to-pay threshold (λ), the net monetary benefit (NMB) was defined as NMB=λ*ΔE – ΔC. When NMB>0, the treatment is considered cost-effective.

Pricing Scenario

We included a pricing scenario based on patent expiration of tadalafil and vardenafil, causing generic competition and entailing lower pharmacy retail price. In the base case model, we assumed that tadalafil and vardenafil would be patented for 10 years (assuming loss of exclusivity (LOE) to occur sometime after the model duration), whereas sildenafil would be off patent, thus using the current stepwise price reduction (69%) throughout the model.

In the price scenario, the pharmacy purchase price (PPP) of tadalafil and vardenafil was also reduced by 69% throughout the model. This provides the possibility to compare the cost-effectiveness of every PDE5 inhibitor regardless of any pricing reduction that currently only applies to sildenafil. After the price reduction, the pharmacy retail prices of tadalafil and vardenafil were calculated by including pharmacy margin and tax to the PPP, as suggested by NoMA [25].

Sensitivity analyses

Several one-way sensitivity analyses were performed, together with several probabilistic sensitivity analyses (PSAs). In addition, scenario analyses was included to explore how removing and changing some of the key model structure parameters would impact the model results in the primary patient population. This included removing the switching and dose optimization options, removing AE outcomes, and limiting the model time horizon to a one-year period. Furthermore, cost-effectiveness acceptability curves (CEACs) were plotted to estimate the (essentially Bayesian) probability of the various PDE5 inhibitors being cost-effective, as a function of the WTP threshold. To assess the expected cost of uncertainty, the expected value of perfect information (EVPI) and the

expected value of partial perfect information (EVPPI) were calculated, providing information on whether further research should be considered.

Software

The cost-effectiveness analysis and subsequent sensitivity analysis was performed in Excel 2016. Macros used to run simulations for the PSA and EVP(P)I were written in Visual Basic.

Input and material

Model inputs were derived from various systematic reviews, Norwegian population-based registers, and additional literature searches.

Systematic searches were conducted for English- and Norwegian-language articles using PubMed, Cochrane Library, and Elsevier. The search strategy included the following keywords: "randomized controlled trial", "discontinuation", "switching", and "erectile dysfunction" in combination with "sildenafil", "tadalafil", "vardenafil", and/or "phosphodiesterase inhibitor". Studies that reported probabilities, costs, and utility scores related to ED and PDE5 inhibitor treatment were assessed based on publication date, relevance to Norwegian conditions, and general data collection strength (e.g., sample size).

Transition probabilities

Table 1 summarizes the strategy-specific parameters and their corresponding monthly probabilities and distributions, as derived from the literature [5, 7, 26, 27]. The most recent network meta-analysis, exploring PDE5 inhibitor treatment efficacy, included 87 trials, with a total of 47,626 patients [5]. From this trial, we derived rates and conditional probabilities of transitions between health states. The response parameter in Table 1 represents patients with treatment efficacy with the respective PDE5-inhibitor treatment (i.e. for patients in the "No ED" and "No ED with AE" health states of the model).

Dose optimization for sildenafil (50 to 100 mg) and tadalafil (10 to 20 mg) were based on a study reporting the proportion of patients who increased their medication dose during the first eight weeks of treatment [28]. It was assumed that the patients only increased the medication dose in the case of insufficient effect with their previous treatment dose (i.e. in the "ED", and "ED with AE" health states). As patients were assumed to only increase their

dose if in the “ED” and “ED with AE” health states (indicating a lack of treatment response), the proportion of individuals increasing their dose was adjusted for the competing risk of being in other health states (so that the total proportion of patients increasing their treatment dose would still amount to the proportions as reported by Eardley I. et al. [28]. For instance, in the study by Eardley I.et al., it was reported that 87 out of 291 patients (30%) on sildenafil increased their dose to the sildenafil 100 mg (high dose) option during the two month dose optimization period, equal to a monthly probability of 16.3% (as reported in Table 1). In the model, this probability was only applied to the patients in the “ED” and “ED with AE” health states (assuming that the patients in the “No ED” and “No ED with AE” health states would not increase their dose). As 16.3% should be the **total** proportion of patients on sildenafil increasing their dose during the first month (and not 16.3% of those in the “ED” and “ED with AE” health states), a conditional probability of transition was calibrated to adjust for the competing risk of being in the “No ED”, “No ED with AE”, “Death”, and “dropout” health states, as well as those patients switching treatment. Adjusting for this risk during the first 2 months of treatment, implied that a total of 73% of the patients who remained in the sildenafil “ED” and “ED with AE” health states would increase their sildenafil treatment dose. This adjustment in the Markov-trace ensured that after the initial two-months dose optimization period, 30% of the patients on sildenafil had increased their dose to the 100 mg option (similarly as reported in the study by Eardley I., et al., with 87/291 patients), all of which being individuals coming from the “ED” and “ED with AE” health states. Dose optimization for vardenafil was not included due to lack of data.

The probability of switching and dropout was acquired through a real-life observational study by Mohee A., et al., using a prospectively accrued database (29). Similarly to the dose optimization option, the patients were assumed to only switch the treatment option if experiencing lack of efficacy (represented by the “ED” and “ED with AE” health states), in addition to the “No ED with AE” health state. Therefore, similar to the dose adjustment transition probability, the method of calculated a conditional probability of switching, which adjusted for the competing risk of being in a health state where switching would not apply, was used.

TABLE 1

For more details on the parameters and calculated transition probabilities used in the Markov model, see the online Appendix section A1.

Utilities

Table 2 presents the utility and disutility weights assigned to each particular health state and event. An average utility weight for diabetics was included to adjust the utilities to the diabetic population.

TABLE 2

No specific AEs were reported in any of the identified studies, and so a disutility of stroke was assumed to capture the disutility of the pooled serious AEs. QALY estimates related to AEs were based on a study assessing duration of side effects of sildenafil, tadalafil, and vardenafil [10]. The average duration associated with each AE was multiplied by the disutility of the given AE (summarized in Table 2); this provided an estimate of disutility over time that was subtracted from the overall QALY estimate, producing a measure that contains both treatment benefits and harms. Table A13 in Appendix A4 (online) summarizes the average AE duration associated with the different treatment options. For serious AEs, the average duration was assumed to be one cycle (one month).

Costs

All costs were adjusted from NOK to EUR using the exchange rate of EUR 1.00 to NOK 9.618. Costs of PDE5 inhibitor treatments were estimated for different-sized packages and doses using the pharmacy retail price provided by the NoMA medicine database [37]. It was assumed that patients using a new PDE5 inhibitor (either at the initial time period or when switching medication/dose) started on a 4-tablet pack, and would thereafter buy 12-tablet packs for the remaining treatment period. We included the cost of a GP consultation when: starting on a new treatment (at the initial time period and when switching to another PDE5 inhibitor); increasing the treatment dose (during the dose optimization period); and renewing the prescription, assumed to occur every 12 months (except from those in the "dropout" and "death" states). Cost of transportation to GP/specialist visits was based on an estimate from 2012, adjusted for inflation [38]. To estimate the medication cost per patient, the average annual quantity of doses used per patient was also included, information collected from the Norwegian Prescription Database [39]. Further details on calculations of GP consultation costs and cost parameters can be found in Appendix A5 (Online).

The medicine costs per dose are summarized in Table 3. Note that price reductions on tadalafil and vardenafil have been included, in order to represent expected prices after introducing generic equivalents (following LOE). The percentage of incremental price reduction was identical to observed price reductions for sildenafil (69%) and

included pharmacy margin and tax, as proposed by NoMA [40]. All standard errors for costs were derived using a 20% variation of the deterministic value.

TABLE 3

RESULTS

Cost-effectiveness results

The deterministic cost-effectiveness results for both the primary and secondary patient populations are presented in Table 4.

Tadalafil was dominated in both scenarios (less effective and more costly than sildenafil). In the primary patient population, at a WTP threshold of €25,000, sildenafil was estimated to be the most cost-effective option in both the base case and the price scenario, with ICERs of €4,477 and €8,341, respectively.

For the secondary population, sildenafil was estimated to be the most cost-effective option, with ICERs of €5,526 and €13,250 for the base case and price scenarios, respectively.

TABLE 4

Sensitivity analyses

Table 5 below presents scenario analyses on some of the key model parameters. For the base case scenario, removing the treatment switching option from the model resulted in the greatest ICER impact, with a 6% ICER increase for the tadalafil treatment option, and an ICER reduction of 16% and 13% in the sildenafil and vardenafil treatment options, respectively. In the pricing scenario, changes in the model time horizon had the greatest impact on the cost-effectiveness results. With a 1 year time horizon, the ICER increased with 8% and 14% for the sildenafil and tadalafil treatment options, respectively, and reduced with 4% for the vardenafil treatment option.

Table 5

Furthermore, the sensitivity analyses indicated that the response rate of vardenafil was the most sensitive parameter. If the efficacy of vardenafil treatment was increased by 23%, or if the efficacy of sildenafil was decreased by 27%, vardenafil became the optimal treatment strategy. In the base case scenario, changes from 0.60 to 1.00 in the response rate of tadalafil did not change the optimal strategy (sildenafil) (see Table A17 in the online appendix for more results).

Figure 2 presents the cost-effectiveness acceptability curves (CEACs) for both the primary patient population and for the secondary patient population.

Figure 2

For the primary patient population, the likelihood of being cost-effective varies according to the thresholds, as depicted in Figure 2. Regardless of pricing scenario, a low WTP threshold (WTP<€3,000) favors the no-treatment option. For a WTP threshold greater than €4,500, ED treatment using at least one PDE5 inhibitor provided a higher likelihood for being cost-effective compared to the no-treatment option.

Similar findings were identified for the secondary patient population. Regardless of pricing scenario, a WTP<€3,750 favored the no-treatment option, and for WTP>€5,500, ED treatment using one of the PDE5 inhibitors was more likely to be cost-effective. At a WTP>€14,000, sildenafil was the treatment option that was most likely to be cost-effective, regardless of patient population.

The individual EVPI for the primary patient population in the base case scenario was €240 for a WTP of €5,000 and €140 for WTP of €2,600 and €8,200 in the price scenario. For the secondary patient population, the individual EVPI was €260 at a WTP of €6,500 in the base case scenario while for the pricing scenario it was €150 and €230 for WTP of €3,700 and €13,500, respectively. The EVPPI showed the highest value for utilities and costs for the primary patient population, while for the secondary patient population, the EVPPI for utilities and costs reached a maximum value while the value of information for the transitions were increasing with the WTP (see figure A2 in the online Appendix for more information).

DISCUSSION

Main findings

To the best of our knowledge, this is the first CUA comparing three separate PDE5 inhibitors. We included data from the most recent studies, and we used more advanced methods than prior analysis. Furthermore, we assessed the cost-effectiveness of treating a specified subpopulation of ED patients: ED patients with diabetes. We found that the cost-effectiveness of all PDE5 inhibitors were favorable compared to the no-treatment option. Given a WTP>€14,000, the sildenafil treatment was identified as the most cost-effective treatment strategy for all pricing scenarios and for both patient populations. The uncertainty analysis did not alter the conclusions, although (depending on the WTP) further research to reduce uncertainty could potentially be cost-effective.

The scenario analyses showed that the preferred treatment option could change, as the cost-effectiveness of the three treatment strategies varied according to scenario. As an example, the scenario using a 1-year time horizon indicated a significant ICER increase for the more costly sildenafil (+8%) and tadalafil (+14%) treatment options, and an ICER decrease for the less costly vardenafil option (-4%). This means that a higher WTP would most likely be required for the sildenafil treatment option to be considered cost-effective, especially in the diabetic population when compared to the vardenafil treatment. However, the overarching results was robust as the scenario analysis still indicated that PDE5-inihibitors was likely to be a cost-effective treatment option in ED patients when compared to a "no-treatment" option (assuming a WTP threshold > €15,000).

Based on the EVPI and EVPPI, we found that the value of information was higher for the secondary patient population (ED with diabetes). The result of the EVPPI analysis indicated that the seemingly-continuous increase in value of information was related to the uncertainty of treatment with tadalafil, which at a high WTP threshold no longer had any barrier for cost-effectiveness related to medication cost. This means that the uncertainty in transition parameters (e.g. efficacy outcomes) could potentially make tadalafil the optimal treatment strategy.

Previous research

A CUA of sildenafil compared to papaverine-phentolamine injections as a second-line treatment for ED found that sildenafil was cost-effective, with an ICER of £3,639 [16]. Adjusted for inflation, this translates into an ICER of €7,915. Another cost-effectiveness analysis on sildenafil compared to no-drug therapy concluded that the ICER of

sildenafil treatment was $11,290 [15]. Converted to EURO and scaled for inflation, this ICER translates into €19,640. In these studies, the medication costs were considerably higher than in our study, which might be due to the fact that sildenafil at that time was under patent protection, causing a considerably higher pharmacy retail price. Furthermore, the study by Smith et al. included estimates on AEs based on insufficient data, which were therefore assumed to be more severe than the current empirical studies have shown.

The most recent CUA was a study performed by Mittmann et al. in a Canadian setting [17]. They assessed the cost-effectiveness of sildenafil compared to surgical intervention and vacuum constriction devices in treatment of an ED population with spinal cord injury. They found that sildenafil was the dominant strategy, with an ICER of less than CAN $20,000. Converted to EURO and adjusted for inflation, the ICER of sildenafil translates into €20,906 when compared to vacuum constriction devices.

Model validity

The model was validated according to standard methods in order to show the precision of the model [41]. Internal validity implies that the mathematical calculations were correct and consistent with the specification of the model. Several standard methods were applied to determine the internal validity. Face validity was determined by inspecting whether the results makes sense and can be explained at an intuitive level. Although no other identified studies have explored the cost-effectiveness of several PDE5-inhibitors, the disease-specific model structure was comparable to other studies where fewer treatment options were analyzed [15]. Furthermore, referred to as cross-validity, we validated the model findings with results from previous analyses on the field, as shown above, indicating similar results of PDE-inhibitors being cost-effective when compared to no-treatment, or other non-PDE5 inhibitor treatments [15, 16, 17]. This further demonstrates that PDE5-inhibitors in treating ED are likely to be a cost-effective treatment option.

Limitations

This study has a series of limitations, mostly related to parameter uncertainty, assumptions, and structure of the model. One limitation is related to the comparators used in the CUA. If a series of alternative second-line treatments were included in the analysis, they could have potentially made the PDE5 inhibitors appear less cost-effective. Some of these second-line treatment modalities include hormonal treatment, vacuum constriction devices, intracavernosal injections, and surgical intervention. However, these treatments are unlikely to be cost-

effective, as they are often more costly than PDE5 inhibitors and are associated with specific, likely considerable AEs (e.g., local pain, fibrosis) [42]. This CUA only included sildenafil, tadalafil, and vardenafil for two reasons: first, these PDE5 inhibitors are the most commonly-used ED treatments; second, few studies examine treatment efficacy and harms of other PDE5 inhibitors, which were crucial in this CUA.

The time horizon of the model was selected at 10 years. This was thought to be adequate, as all costs and benefits from PDE5 inhibitor treatment occur mostly within the same treatment cycle; that is, no long-term benefit or costs were expected from PDE5 inhibitor treatments. Theoretically, a shorter time horizon of one year would also capture similar results.

Another limitation was related to the transition probabilities and utility weights used in the analyses. Most inputs were based on estimates from foreign studies, which were adapted to simulate Norwegian conditions. This may unduly affect the findings, as the Norwegian ED population is not necessarily comparable to those included in other studies. However, the benefit of using the estimates is that several studies were conducted that could be applied to the model (giving better model structure and less uncertainty).

Several AEs that were not included in the state-transition Markov model might be related to PDE5 inhibitor treatment. These AEs were not included since they were supported by very little empirical evidence. However, the incidence of these treatment-related AEs were all shown to be non-significant compared to placebo treatment, and most were generally mild in nature. For this reason, the exclusion of these AEs was not expected to impose any significant impact on cost-effectiveness results of the model.

Another limitation stems from the "memoryless" property of state-transition models – that is, these models assume that transition probabilities to the next state depend only on the current state, regardless of prior states. This was reflected in patients who switched PDE5 inhibitor treatment or increased their dose. It would have been reasonable to assume that patients switching treatment due to insufficient effectiveness were also more likely to have insufficient effects with the new treatment. However, since the state-transition model has no memory, all individuals within any health state were assumed to all have the same transition probabilities, regardless of any previous history with unsuccessful treatment.

Although parameter uncertainty has been widely explored through PSAs, other sources of uncertainty could potentially deteriorate the model accuracy. Structural uncertainty (such as the structure of the state-transition model, type of health states, and events) could potentially influence model results, but it was not included in the analysis [43].

The state-transition model was based on results from RCTs; therefore, the analysis was restricted to the average age of the trial populations (age 55). Although the results may have been different for other age groups, no studies were identified that report how treatment outcomes depend on age. For this reason, the cost-effectiveness outcome of this study is expected to represent all age groups.

Health utility estimates were derived from studies using a combination of multi-attribute utility instruments (EQ-5D) and valuation methods (time-trade-off). The disutility estimates used for AEs were derived from a variety of patient groups and studies, not specifically from ED patients. This may be problematic, as the disutility experienced by an ED user may be different from the estimates used in this study.

Despite the above limitations, this analysis provided important contributions to the cost-effectiveness field of PDE5 inhibitors and the treatment of ED. The results and the model structure that was developed can be used in further cost-effectiveness analysis of PDE5 inhibitors concerning different treatments, patient populations (sub-groups), and countries.

CONCLUSION

This study was prompted by the practical need to identify the cost-effectiveness of PDE5 inhibitors in treating ED. We modeled three ED treatment strategies in a Norwegian context: starting on sildenafil treatment, starting on tadalafil treatment, and starting on vardenafil treatment. As the prices of tadalafil and vardenafil are expected to be reduced in the future, a pricing scenario was analyzed to give an indication of possible cost-effectiveness developments resulting from future price reductions and from introduction of generic equivalents.

Given the existing evidence, sildenafil treatment of ED was a cost-effective option compared to tadalafil, vardenafil, and no treatment, with costs per QALY below most proposed WTP thresholds. Sildenafil treatment remained the optimal strategy even after an expected price reduction on tadalafil and vardenafil was included. Treating a diabetic population was less cost-effective for all PDE5 inhibitors and was associated with greater

uncertainty as to the optimal treatment strategy. However, sildenafil remained the optimal treatment strategy in the diabetic population. Further research to reduce uncertainty around the optimal choice among PDE5 inhibitors could be cost-effective, but the cost-effectiveness of PDE5 inhibitors compared to a no-treatment option is unlikely to change with more information.

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Table 1. Strategy-specific monthly probabilities for sildenafil, vardenafil and tadalafil. Total number of patients included in the studies was represented as observations. AE = adverse event

Sildenafil (50/100 mg)				
Parameter	Probability	Observations	Distribution	Source
Response 50mg	0.775	2,158	Beta	(1)
Response 100mg	0.753	624	Beta	(1)
Response among diabetic users	0.610	351	Beta	(1)
Treatment related AE	0.191	2,907	Beta	(2)
Increase in dose (50mg to 100mg)	0.163	291	Beta	(3)
Switch to tadalafil (10mg)	0.0016	696	Dirichlet	(4)
Switch to vardenafil	0.0004	696	Dirichlet	(4)
Tadalafil (10/20 mg)				
Parameter	Probability	Observations	Distribution	Source
Response 10mg	0.646	780	Beta	(1)
Response 20mg	0.662	2,196	Beta	(1)
Response among diabetic users	0.600	145	Beta	(1)
Treatment related AE	0.189	403	Beta	(2)
Increase dose (10mg to 20mg)	0.277	291	Beta	(3)
Switch to sildenafil (50mg)	0.0010	990	Dirichlet	(4)
Switch to vardenafil	0.0007	990	Dirichlet	(4)
Vardenafil (10 mg)				
Parameter	Probability	Observations	Distribution	Source
Response 10mg	0.655	4,511	Beta	(1)
Response among diabetic users	0.532	154	Beta	(1)
Treatment related AE	0.174	3,392	Beta	(2)
Switch to sildenafil (50mg)	0.0013	163	Dirichlet	(4)
Switch to tadalafil (10 mg)	0.0045	163	Dirichlet	(4)

Table 2. Utility weights assigned to the different health states and events. ED = erectile dysfunction, AE = adverse event

Parameters	Deterministic value	Standard error	Distribution	Source
Utility				
ED	0.89	0.022*	Lognormal	[30]
No ED	0.96	0.008*	Lognormal	[30]
Diabetes	0.82	0.037	Lognormal	[31]
Disutility				
Headache	0.14	0.027	Lognormal	[32]
Dyspepsia	0.08	0.013	Lognormal	[33]
Visual impairment	0.03	0.010	Lognormal	[34]
Flushing	0.17	0.033*	Lognormal	[10]
Back pain	0.05	0.021	Lognormal	[35]
Serious AE	0.30	0.005	Lognormal	[36]

*estimate based on 20% of the deterministic value

Table 3. Cost per-dose with sildenafil, tadalafil and vardenafil presented as EURO. Prices on different sized packages (4-tablet pack and 12-tablet pack) are included for all three treatment options. Prices of different medication strengths are included for sildenafil and tadalafil. SE = standard error

Sildenafil				
Cost parameters	Cost per-dose*	SE	Distribution	Source
50 mg 4-tablet pack	3.37	0.67	Gamma	[35]
50 mg 12-tablet pack	2.82	0.56	Gamma	[35]
100 mg 4-tablet pack	3.83	0.77	Gamma	[35]
100 mg 12-tablet pack	3.05	0.61	Gamma	[35]
Tadalafil				
Cost parameters	Cost per dose (price scenario)*	SE (price scenario)	Distribution	Source
10 mg 4 tablet pack	12.68 (4.56)	2.53 (0.90)	Gamma	[35]
10 mg 12 tablet pack	N/A	N/A	Gamma	[35]
20 mg 4 tablet pack	12.68 (4.56)	2.54 (0.90)	Gamma	[35]
20 mg 12- tablet pack	11.95 (3.96)	2.39 (0.79)	Gamma	[35]
Vardenafil				
Cost parameters	Cost per dose (price scenario)*	SE (price scenario)	Distribution	Source
10 mg 4 tablet pack	4.68 (2.10)	1.00 (0.43)	Gamma	[35]
10 mg 12 tablet pack	4.37 (1.56)	0.87 (0.31)	Gamma	[35]

**cost per dose expresses today's pharmacy retail price for a single dose.*

Table 4. Cost-effectiveness result for both the primary group of patients and the diabetic population. Both direct and indirect costs are included (societal perspective) and discounted at 4 percent per year. Time horizon is 10 years. All costs are presented as EUR

Treatment strategy	**Total costs**	**Total QALYs**	**Incremental cost (ΔCost)**	**Incremental effectiveness (ΔQALYs)**	**ICER (ΔCost/ΔQALY)**
General population					
Base case					
No-treatment	-	7.166	-	-	-
Sildenafil (50/100 mg)	1,542	7.510	1,542	0.344	4,477
Vardenafil (10 mg)	1,739	7.455	198	-0.056	Dominated*
Tadalafil (10/20 mg)	3,924	7.459	2,382	-0.051	Dominated*
Price scenario					
No-treatment	-	7.166	-	-	-
Vardenafil (10 mg)	867	7.455	867	0.289	3,019
Sildenafil (50/100 mg)	1,335	7.510	463	0.055	8,341
Tadalafil (10/20 mg)	1,573	7.459	238	-0.051	Dominated*
Diabetic population					
Base case					
No-treatment	-	5.717	-	-	-
Sildenafil (50/100 mg)	1,530	5.993	1,530	0 2768	5,526
Vardenafil (10 mg)	1,744	5.959	25	-0.0339	Dominated*
Tadalafil (10/20 mg)	3,970	5.989	2,440	-0.0041	Dominated*
Price scenario 2					
No-treatment	-	5.717	-	-	-
Vardenafil (10 mg)	874	5.959	874	0.2429	3,597
Sildenafil (50/100 mg)	1,323	5.993	449	0.0339	13,250
Tadalafil (10/20 mg)	1,591	5.989	268	-0.0041	Dominated*

*An alternative strategy is dominated if it is less effective and more costly than another alternative (producing negative ICER).

Table 5. Scenario analyses exploring how changes in some of the key model structure parameters would impact the results of the primary patient population.

	ICER vs "no- treatment" (%Δ vs base case)		
Parameter	**Sidelanfil**	**Tadalafil**	**Vardenafil**
Base case scenario			
Time horizon reduced to 1 year	4,316 (-5%)	14,408 (+6%)	5,768 (-5%)
No treatment switching	3,800 (-16%)	14,332 (+6%)	5,330 (-13%)
No dose optimization period	4,401 (-3%)	13,676 (+1%)	6,082 (-0%)
No adverse events	4,415 (-3%)	13,178 (-3%)	5,823 (-4%)
Price scenario			
Time horizon reduced to 1 year	4,241 (+8%)	6,198 (+14%)	2,922 (-4%)
No treatment switching	3,800 (-3%)	5,578 (+3%)	2,666 (-13%)
No dose optimization period	3,797 (-3%)	5,424 (0%)	3,037 (-1%)
No Adverse Events	3,823 (-3%)	5,282 (-3%)	2,919 (-4%)

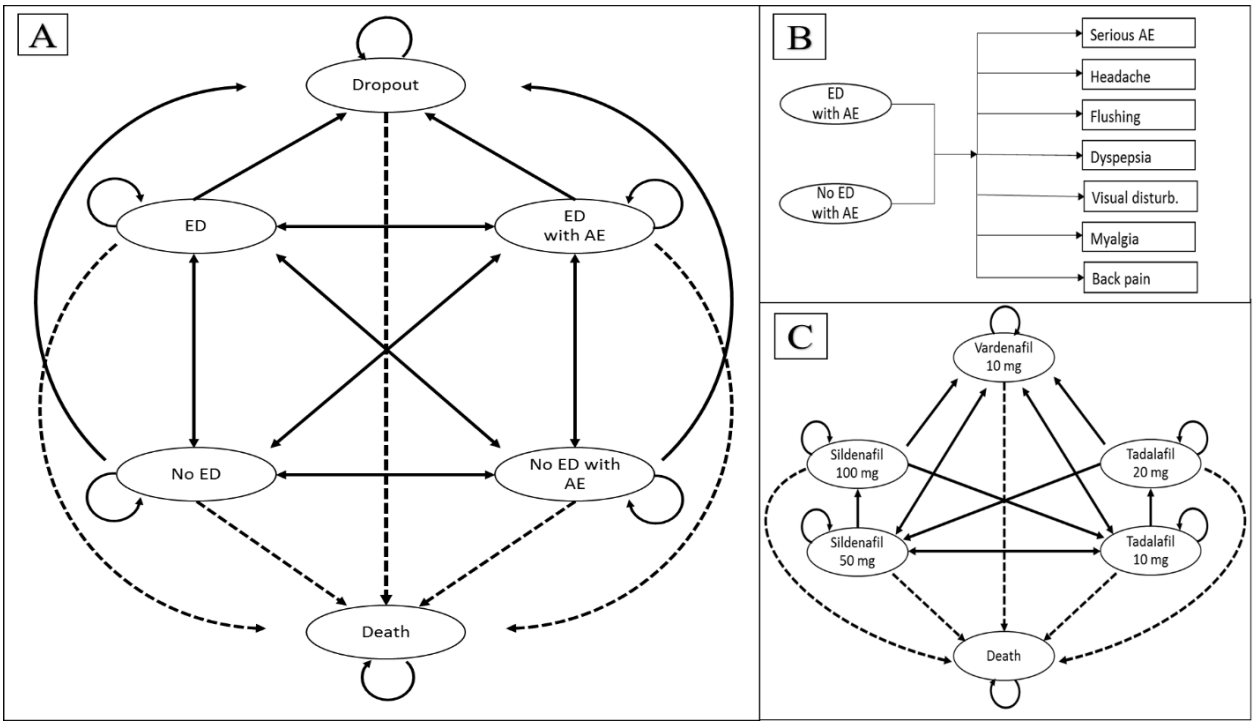

Figure 1. State transition Markov model of PDE5 inhibitor therapy using sildenafil, vardenafil or tadalafil. Circle is state and square is event. Dotted line represents transitions with equal probability. Model A represent a "treatment specific" model. Model B represent experienced adverse events. Model C represent movement in-between medications (switching). All patients start in the "ED" health state. ED = Erectile dysfunction, AE = Adverse events.

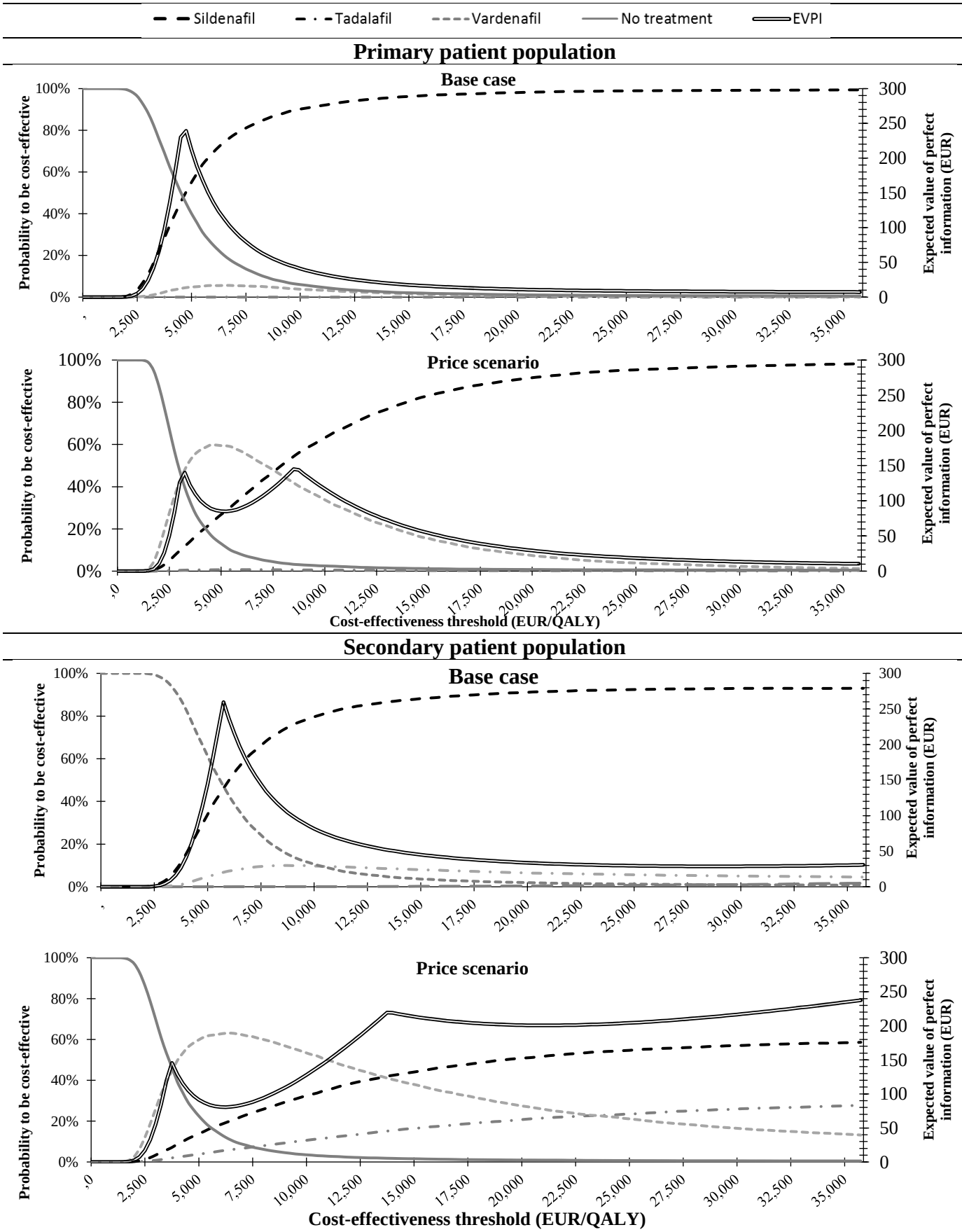

Figure 2. Cost-effectiveness acceptability curves (CEACs) and expected value of perfect information (EVPI) for the choice of erectile dysfunction treatment strategy in the general ED population (primary population) and diabetic patient population (secondary population). EVPI is presented in EUR.