
Article:
Martin, A orcid.org/0000-0002-2559-6483, Payne, R and Wilson, ECF (2018) Long-Term Costs and Health Consequences of Issuing Shorter Duration Prescriptions for Patients with Chronic Health Conditions in the English NHS. Applied Health Economics and Health Policy, 16 (3). pp. 317-330. ISSN 1175-5652

https://doi.org/10.1007/s40258-018-0383-9

Title:

Long term costs and health consequences of issuing shorter duration prescriptions for patients with chronic health conditions in the English NHS

Running heading:

Shorter duration prescriptions for patients with chronic conditions

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Word count: 3,975

ABSTRACT

Background: The NHS in England spends over £9 billion on prescription medicines dispensed in primary care, of which over two thirds is accounted for by repeat prescriptions. Recently, GPs in England have been urged to limit the duration of repeat prescriptions where clinically appropriate to 28 days to reduce wastage and hence contain costs. However, shorter prescriptions will increase transaction costs and thus may not be cost saving. Furthermore, there is evidence to suggest that shorter prescriptions are associated with lower adherence, which would be expected to lead to lower clinical benefit. The objective of this study is to estimate the cost-effectiveness of 3-month versus 28-day repeat prescriptions from the perspective of the NHS.

Methods: We adapted three previously developed UK policy-relevant models, incorporating transaction (dispensing fees, prescriber time) and drug wastage costs associated with 3-month and 28-day prescriptions in three case studies: antihypertensive medications for prevention of cardiovascular events; drugs to improve glycaemic control in patients with type 2 diabetes; and treatments for depression.

Results: In all cases, 3-month prescriptions were associated with lower costs and higher QALYs than 28-day prescriptions. This is driven by assumptions that higher adherence leads to improved disease control, lower costs and improved QALYs.

Conclusion: Longer repeat prescriptions may be cost-effective compared with shorter ones. However, the quality of the evidence base on which this modelling is based is poor. Any policy rollout should be within the context of a trial such as a stepped-wedge cluster design.

Key Points for Decision Makers:

- Our analyses predict that 3-month repeat prescriptions may be more cost-effective over a lifetime than 28-day prescriptions, indicating that policies which encourage shorter duration prescriptions to reduce costs are not supported by evidence.
- We adapted existing decision models for drugs commonly prescribed to patients with long-term conditions to account for differences in drug dispensing costs, prescriber time, drug wastage and medication adherence.
- The analyses relied on consistent, but poor quality evidence of a positive association between prescription length and adherence. More rigorous assessment of the long term impact of different prescription lengths is warranted to confirm or refute our modelled analyses.

1. INTRODUCTION

In England, over £9 billion is spent annually by the National Health Service (NHS) on prescription medicines dispensed in primary care.[1] Around two thirds of this expenditure is accounted for by repeat prescriptions, which are issued by GPs to treat chronic health conditions without the need for a patient consultation.[2]

Recent policy changes in some areas of England have advised General Practitioners (GPs) to reduce the duration of repeat prescriptions issued to patients with chronic health conditions, typically from 3-months to 28-days.[3-6] The rationale for the policy change was to reduce medicines waste and thus generate cost savings. Published estimates, including those of the National Audit Office (NAO), suggest that up to £300m of prescription medications are wasted in England each year, of which half may be avoidable.[7, 8] Nevertheless, the policy may have overlooked some potential disadvantages of shorter prescriptions, including additional transaction costs incurred by the NHS (e.g. through increased GP time to issue prescriptions and dispensing fees to pharmacists) and the inconvenience of additional trips to the pharmacy (which may lead to reductions in patient satisfaction and additional costs to patients, e.g. related to lost productivity).[9-12] Furthermore, the relationship between prescription duration and adherence to treatment (i.e. whether patients take their drugs as directed by their GP) should also be considered, since any detrimental impact on health, including the risk of adverse health events, would lead to increased healthcare costs in the longer term.

A recent systematic review identified consistent (but poor quality) evidence that longer prescription duration was associated with increased adherence but increased wastage.[13] An analysis of UK primary care data confirmed the positive relationship between prescription duration and wastage.[14] However, this also showed that reductions in transaction costs

associated with longer prescriptions more than compensated for the costs of increased wastage (at least in the case studies examined). The review[13] noted (1) a shortage of studies examining the long term relationship between prescription duration and health outcomes (mean follow-up of previous studies was 20.3 months), (2) that existing studies were entirely US based and so of questionable relevance to the UK setting, (3) only one examined any impact on health outcomes,[15] and (4), none reported outcomes in terms of QALYs gained.

Therefore, the purpose of this paper is to estimate the longer term costs and health consequences and hence incremental cost-effectiveness associated with 3-month and 28-day repeat prescriptions for patients with stable, chronic conditions requiring one or more repeat prescriptions in the primary care setting.

2. METHODS

We selected three case studies of drugs typically prescribed in primary care for chronic, stable conditions. These were (1) antihypertensive medications for prevention of cardiovascular events in patients with essential hypertension, (2) metformin to improve glycaemic control in patients with type 2 diabetes, and (3) selective serotonin reuptake inhibitors (SSRIs) for depression.

We first identified and then adapted existing decision analytic models used to assess the clinical and cost-effectiveness of relevant pharmaceutical products by the National Institute for Health and Care Excellence (NICE). We then identified data on (1) the relationship between prescription length and adherence in patients with chronic health conditions (from the systematic review [13]), (2) the relative treatment effects of the drugs vs placebo (where existing analyses did not compare versus placebo) (from relevant NICE guidance), (3)

transactions costs (dispensing fees and prescriber time) and (4) cost of drug wastage (from an analysis of UK primary care data [14]).

Models were adapted to calculate the expected cost and QALYs gained from 3-month or 28-day repeat prescriptions. A general overview is shown in Figure 1; the long term cost and QALYs associated with a particular treatment were assumed to represent perfect adherence and those of placebo to represent zero adherence. Given that the systematic review[13] showed 3-month repeat prescriptions were associated with higher adherence than 28-day prescriptions, in the absence of evidence to the contrary, we assumed the 3-month repeat prescriptions would yield the expected cost and QALYs associated with perfect adherence (i.e. p=1 in Figure 1), and 28-day be equal to those multiplied by the relative risk of adherence. Plausible values for the relative risk for each of the three groups of commonly prescribed medications were extracted from studies identified in the systematic review that had examined medications which could be reasonably categorised into those three groups. [13] Where there was more than one estimate, or a range of estimates, these were subsequently used in sensitivity analyses.

A summary of the methods used in each case study is provided in Table 1. Incremental cost effectiveness ratios (ICERs) were calculated (based on the incremental costs and QALYs of treatment with 3-month versus 28-day prescriptions). Net benefit and incremental net benefit (INB) were also reported. This assumes a threshold value of the decision maker's willingness to pay for a QALY of £20,000 (the lower end of the cost effectiveness threshold over which treatments are less likely to be recommended for use in the NHS).[16] The perspective of the evaluation was costs to the NHS in England and all cost data are reported in 2015/6 British Pounds Sterling. Costs were inflated when necessary to 2015/6 levels using the Personal Social Services Research Unit (PSSRU) Hospital and Community Health Service indices.[17]

Specific methods for each case-study follow, with summaries of the original source models provided in Table 2, and of the identified data and key assumptions in Table 3. Some additional details for is also provided in Appendices 1, 2 and 3 (Electronic Supplementary Materials).

2.1 CASE STUDY 1: Antihypertensive medications for prevention of cardiovascular events in patients with essential hypertension

Stage 1: Identify decision model

Relevant NICE guidelines on pharmacological interventions for adults with essential hypertension were reviewed. The most recent NICE guidance (CG127, updated 2011) included a Markov model which assessed the cost effectiveness of four groups of alternative antihypertensive medications (angiotensin converting enzyme inhibitors [ACEIs]/angiotensin II receptor blockers [ARBs], beta blockers, calcium channel blockers, thiazide type diuretics) and a 'no treatment' comparator (Table 2).[18]

The model has seven discrete health states (event free/well, myocardial infarction (MI), unstable angina, stroke, diabetes, heart failure and death, Figure 2). The likelihood of moving between states during each model cycle is determined by transition probabilities which vary according to patient characteristics (e.g. age, sex, ethnicity and baseline health event risks) and the prescribed medication. Transition probabilities in the 'no treatment' arm as well as relative risks for each treatment had been extracted from relevant literature. Health state utilities had been derived from published studies and used to calculate QALYs. Annual costs associated with each health state (from the NHS perspective), and the costs of medications, had been

identified from various sources (e.g. British National Formulary, BNF) and used as inputs in the model. (Table 2).[18]

Stage 2: Identify additional data

In the systematic review,[13] two studies by Hermes et al. 2010 and Taitel et al. 2012 reported the relative risk of being adherent for longer versus shorter duration prescriptions for antihypertensive medications.[19, 20] No primary studies nor decision models were identified examining the relationship between prescription length (or adherence) and health outcomes. [13]

It was not necessary to identify additional input data on the costs and health consequences of zero adherence since the source model included a 'no treatment'/placebo comparator. The cost of dispensing fees identified from the latest NHS Drug Tariff [21] and the cost of prescriber time and drug wastage associated with different duration prescriptions for antihypertensive medications were identified in the analysis of UK primary care data (Table 3).[14]

Stage 3: Adapt existing model

Modifications to the structure of the source model were not required as it already examined the costs and consequences of the main groups of antihypertensive interventions currently prescribed in general practice, and included a 'no treatment' comparator.

First, the model was replicated and run to assess the lifetime expected costs and QALYs associated with a weighted average of antihypertensive treatments and with placebo (i.e. representing 'perfect' adherence with antihypertensives and zero adherence as illustrated in Figure 1). As in the base case analysis used in the source model, the cohort used in the analysis was based on a 65-year-old male with an annual cardiovascular disease risk of 2%, heart failure risk of 1% and diabetes risk of 1.1%. Second, we conducted two alternative analyses to

incorporate different adherence levels associated with 3-month and 28-day prescriptions, described in more detail below.

Antihypertensives versus 'no treatment'

The source model estimated a cost of £5,185 and 9.57 QALYs for 'no treatment'. A 'typical treatment' comparator was created as a weighted average of the costs and QALYs associated with each of the four groups of antihypertensive medications. The weights were assigned from total numbers of items dispensed in the community in 2014 (the latest available data) for each antihypertensive class (Appendix 1, Table A1). [22] For this 'typical treatment' comparator, the total costs were £4,563 and 10.16 QALYs. This yielded an ICER of £-1,062 (treatment dominates 'no treatment', Table 4).

3-month versus 28-day prescribing of antihypertensives

We conducted two analyses representing alternative scenarios. In both cases we first added in the transaction and drug wastage costs (Table 3). For the 3-month arm this equated to an extra £21.01 per annum (=[dispensing fees (£0.90) + prescriber time (£3.77) + wastage costs (£0.51)]×[365/90]), and in the 28-day arm, £61.68 (=[dispensing fees (£0.90) + prescriber time (£3.76) + wastage costs (£0.07)]×[365/28]).

In the first analysis, we assumed the costs and outcomes associated with 3-month prescriptions were equal to the cost and outcomes associated with 'weighted treatment', i.e. £4,563 and 10.16 QALYs, (to which the transaction and drug wastage costs were added). In the 28-day arm, the total costs and QALYs were a weighted average of the QALYs in the 'typical treatment' and the 'no treatment' comparators, as described in the Methods section. The weighted average was calculated using evidence from the studies by Hermes et al. 2010 and Taitel et al. 2012 on the relationship between prescription length and adherence which reported relative risks of 0.92

and 0.85 respectively.[19, 20] We report analyses using both sources separately, as well as further analyses using the highest and lowest 95% confidence limits of the two sources (lowest lower bound, Taitel et al. 2012, RR=0.846, highest upper bound Hermes et al. 2010, RR=0.928) to provide a plausible range of ICERs and INB.

In the second analysis, instead of adjusting overall costs and QALYs, we adjusted the relative risks of the transition probabilities by the adherence. For example, the relative risk of MI assumed with 3-month prescriptions for beta-blockers is 0.86 (Appendix 1, Table A2). The relative adherence with 28-day vs 3-month prescriptions is 0.85,[20] so the relative risk of MI with 28-day prescriptions is 0.88 (=1-[1-0.86]×0.85).

2.2 CASE STUDY 2: Metformin to improve glycaemic control in patients with type 2 diabetes

Stage 1 and 2: Identify decision model and additional data

Details of model and data identification (stages 1 and 2 of Table 1) are in Appendix 2.

Stage 3: Adapt existing model.

We focused on the impact of different prescription lengths at the initial therapy stage (people failing to manage their condition on diet and exercise alone) comparing metformin with placebo (two of the seven comparators in the original model). Metformin was chosen for use in this case study as it is current first-line practice. The existing structure of the model and all model inputs remained unchanged, since the identified model already examined the costs and consequences of a wide range of pharmacological interventions for type 2 diabetes which are currently prescribed in general practice in the UK.

Metformin versus 'no treatment'

Lifetime costs and QALYs for metformin, estimated using the original source model were £19,90 and 9.033 respectively, compared with £20,722 and 8.912 for placebo (assumed to represent no treatment) (Table 5). Metformin therefore dominates placebo. These results were driven by higher risk of diabetes-related complications (including amputation, blindness, renal failure, heart disease and stroke) and higher treatment costs due to more rapid progression to later-stage intensification therapies (where patients received >1 non-insulin based therapy) with placebo.

3-month versus 28-day prescribing of metformin

As per case study 1, we assumed 3-month prescriptions yielded equivalent costs and outcomes to the metformin treatment arm in the source model (i.e. p=1 as per Figure 1). To this was added additional annual transactional and drug wastage costs for 3.8 years, the period of time the average patient received initial treatment (monotherapy, where metformin was the only antidiabetic drug).

For the 28-day prescriptions, we took a weighted average of the costs and QALYs of the metformin and placebo arms according to the relative risk of being adherent reported by Hermes and Taitel, which were 0.891 and 0.863 respectively.[19, 20] These are reported as two separate scenario analyses. The total costs and QALYs for the 28-day prescriptions in the first scenario are calculated as 0.891×Metformin arm costs or QALYs + 0.109×placebo arm costs or QALYs. To these calculated total costs were added the additional transaction and drug wastage costs for the average initial treatment period (3.64 years in the first scenario). As per case study 1, we also explored the lower and upper 95% confidence limits (lowest lower bound, Taitel, RR=0.851, highest upper bound Hermes, RR=0.926).

2.3 CASE STUDY 3: Selective serotonin reuptake inhibitors (SSRIs) for depression

Stage 1 and 2: Identify decision model and additional data

Details of model and data identification (stages 1 and 2 of Table 1) are in Appendix 3.

Stage 3: Adapt existing model.

In this case study, we maintained the overall model structure since the identified model had recently been updated by NICE in 2016 and already examined the costs and consequences of antidepressants currently prescribed in general practice. However, whereas the original treatment arms emanating from the decision node in the model were two comparable pharmacological interventions (or a pharmacological intervention with and without CBT), in our adapted model (Appendix 3, Figure A3.1), we substituted instead 3-month and 28-day prescribing of a 'typical' SSRI.

The unit cost data was based on a weighted average of the costs associated with ten (generic and branded) SSRIs. The weighted average was calculated using unit cost data from the Prescription Cost Analysis (published by NHS England) which showed the total number of items dispensed in the community in 2014 for each group of medications.[22] For the 3-month and 28-day arms of the decision tree, we added the appropriate transaction and wastage costs to these (weighted average) SSRI unit costs.

The health consequence data for our 'typical' SSRI was based on data reported in the NICE clinical evidence review on the absolute risk of dropout, no remission and relapse for a placebo arm, and the relative risk for an escitalopram treatment arm. These data were used to calculate the probability nodes in the decision tree where the placebo arm represented our zero adherence scenario and the escitalopram treatment arm represented our perfect adherence scenario (Appendix 3, Table A3.1). Since the NICE guideline development group concluded that there was sufficient doubt about the clinical importance of differences between antidepressant

treatments to not justify the development of recommendations for specific drugs,[23] we did not examine data on the relative efficacy of other antidepressants compared to escitalopram.

Replicating the approach taken by NICE using the source model, we reported the model outputs in terms of the total costs and QALYs of the two arms of the decision tree for two separate cohorts of 100 patients with moderate and severe depression (Table 6).

SSRIs versus placebo

For patients with moderate and severe depression, SSRI treatment was less costly (£1,907.79 versus £2,039.94 per patient in the case of moderate depression) than placebo with higher QALY gains (0.63 versus 0.61 in the case of moderate depression, Table 6). The INB per patient for moderate and severe depression was estimated at £467 and £529 respectively.

3-month versus 28-day prescribing of SSRIs

As per the other case studies, costs and outcomes for the 3-month prescriptions are assumed to be the same as the treatment arm. Those for the 28-day treatment arm were calculated using a weighted average of the cost and QALYs associated with perfect and zero adherence (based on the evidence from studies on the relationship between prescription length and adherence identified in the systematic review [13]).

Two relevant studies, by Pfeiffer and Taitel,[20, 24] reported relative risks of 0.542 and 0.748 respectively. We reported results with these point estimates separately, as well as at the lowest lower 95% confidence limit (Pfeiffer, RR=0.540) and highest higher limit (Taitel, RR=0.780) to define a plausible range of ICERs and INB.

3. RESULTS

In all three case studies for all scenarios, longer prescriptions were both cost-saving and led to higher QALYs gained. In case study 1 (antihypertensives), the INB per patient ranged from £1,470 to £2,571 (Table 4). In case study 2 (metformin), 3-month prescriptions were less costly and yielded higher QALYs than 28-day prescriptions, with expected INB per patient of between £312 and £555 (Table 5). Finally, in case study 3 (SSRIs), for both moderate and severe depression, the ICERs remained negative (3-month prescriptions were cost saving and QALY-enhancing). The INB per patient ranged between £378 and £496 for moderate depression and £427 and £560 for severe.

4. DISCUSSION

Principal findings

The main finding was that longer, 3-month repeat prescriptions are associated with lower lifetime costs and higher QALYs when compared with shorter, 28-day prescriptions. The main driver for this finding was improved adherence in the 3-month scenarios, which was grounded in the evidence from all studies of the relationship between prescription duration and adherence identified in the systematic review.[13] The lower transaction and drug wastage costs reported in the analysis of primary care data[14] also contributed to the finding. Although these immediate cost savings are smaller in magnitude than the longer term benefits arising from improved adherence, they might nonetheless be more pertinent to those making prescribing decisions. Furthermore, it is probable that patients would favour longer prescriptions, at least from the perspective of limiting the frequency of pharmacy visits.

As a result, 3-month prescriptions dominate 28-day prescriptions, with positive INB associated with the 3-month prescriptions. For example, the plausible range of INB (to the NHS) per patient with hypertension receiving treatment for the secondary prevention of cardiovascular events was £1,575 to £2,571. Data from the Health Survey for England shows that 14% of men and 15% of women are currently prescribed antihypertensives specifically for hypertension.[25] Thus there may be significant potential for (long term) cost savings and health gain if these patients were routinely issued 3-month duration repeat prescriptions. This finding was consistent across all three case studies, despite differences in the nature of the treatments. Whereas two case studies focused on the prevention of future ill-health (e.g. cardiovascular events), so increased adherence reduced the expected costs of health complications later in life, the other case study examined SSRI treatment for moderate and severe depression, a chronic or episodic condition. In this case, lower healthcare costs were associated with longer duration prescriptions due to reductions in, for example, the likelihood of requiring additional care during the initial treatment phase as a hospital inpatient.

Our remit was to explore the implications of longer prescription lengths for chronic stable disease. Such treatments tend to be dominant (both less expensive and yielding greater QALYs) compared with placebo as they tend to be low cost drugs with potential to prevent significant life-changing events such as MI or stroke in the future. This was indeed the case in our three case studies. For non-dominant examples, as long as perfect adherence is cost-effective, any partial adherence will also be cost-effective conditional on a linear dose/response relationship. Exploration of this is beyond the scope of this analysis, but drugs requiring close to perfect compliance for any effect to be observed are unlikely to be suitable for longer prescriptions on cost-effectiveness grounds.

Comparison with existing studies

In a recent economic evaluation of a pharmacist-led intervention which supports people starting new medications for long term conditions, decision analytic models were used to assess the lifetime cost and health consequences arising from improved adherence.[26] However, to the best of the authors' knowledge this is the first study to use decision modelling to assess the impact of prescription duration on longer term costs and QALYs.

A number of other observational studies have examined the cost impact of different prescription lengths. A negative relationship between costs and prescription length was found in four of five studies identified [20, 27-29] but the relationship arose for different reasons. The four observing a negative relationship had examined the costs (to third party payers in the US) over a short time horizon. The cost savings arose from reductions in administrative costs of prescribing medication (e.g. dispensing fees). However, these studies did not account for changes in wider healthcare expenditure which would result, particularly in the longer term, from the changes in health status associated with different adherence levels.

The fifth identified study did include those wider costs and showed a positive relationship between prescription length and costs.[30] One explanation could be that healthcare expenditures were examined only over a short time horizon, whereas (two of) the case studies presented in this article examined lifetime costs, focusing on prevention of future cardiovascular events. It should also be noted that all the previous studies were US based and generally from a particular payer's perspective (e.g. Veterans Affairs or Medicaid) which may not be directly comparable to the UK setting.

Limitations

The three case studies presented in this article are based on relatively straightforward adaptions of existing, good quality decision models, all of which have been used to inform policy in the recent past. We chose these models (rather than conducting a systematic review of other

models) as they by definition met NICE's quality criteria and had already been used to inform policy. Basing our analyses on these models thus ensured the case studies were comparable with NICE guidance and hence most policy relevant. Limitations inherent to the specific models are discussed in full detail in the respective guidelines. Therefore, the remainder of this section addresses limitations related to the model adaptations which were made in this study.

First, our findings rely on the positive relationship between prescription length and adherence which was based on studies identified in a systematic review.[13] Whilst all the evidence was consistent, the studies were observational studies, rather than randomised experimental studies, and so are at high risk of bias.

Second, in the absence of data to the contrary, the model adaptations relied on two key assumptions: (i.) treatment effects observed in model active and placebo (no treatment) arms of clinical trials were assumed to represent the maximum effect comparing perfect and zero adherence and (ii.) a linear dose response curve was assumed, thus 50% adherence would generate 50% of the treatment effect. However, since we consistently identified a positive INB associated with longer prescription durations, any change in these assumptions would affect only the magnitude of QALY gains, cost savings and INB. The likelihood that longer prescriptions represent a cost-effective choice would not be affected.

Third, as is common in all decision models which include a 'no treatment' arm, it was necessary to assume that health outcome data from the 'placebo' arm of clinical trials is equivalent to 'no treatment.' However, the placebo effect may lead to an overestimation of the QALYs associated with no treatment. Consequently, the health gain arising from increased adherence in longer prescription durations may have been underestimated.

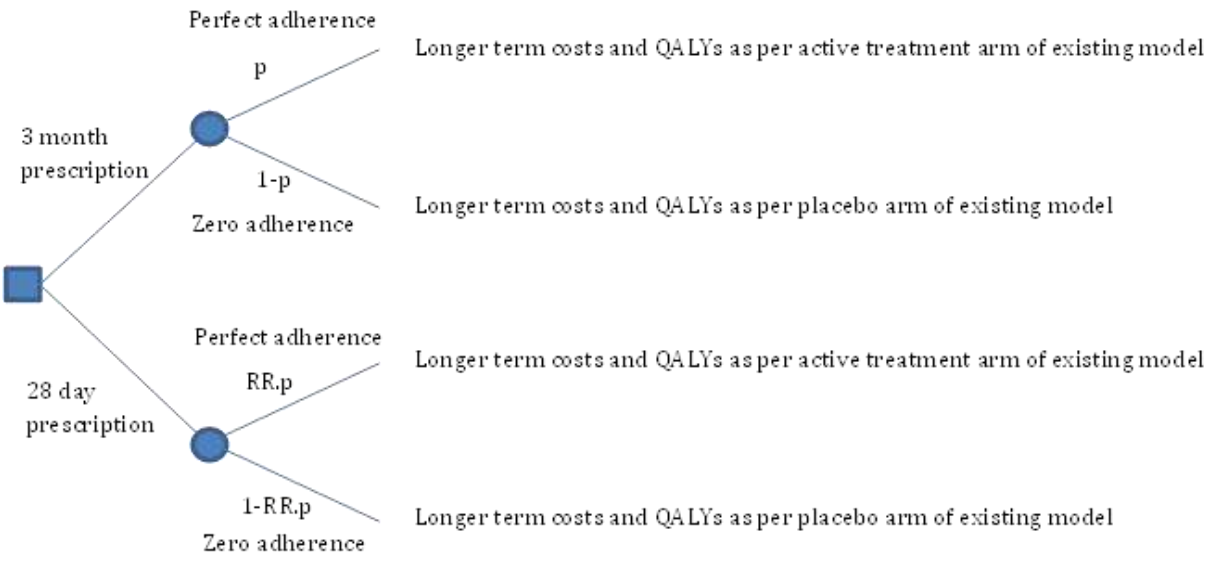
Other limitations were that we assumed adherence was constant over the period of the analysis, and whilst the study took an NHS perspective, any revenue due to the NHS from prescription charges was excluded. However, patients with diabetes are exempt from the prescription charge, and almost 90% of prescriptions dispensed in the community in England do not attract any charge, therefore any revenue would be minimal and thus unlikely to change the results of this study.[31]

5. CONCLUSION

The finding that longer prescriptions may be cost saving to the NHS indicates that the recent policy of encouraging GPs to prescribe 28-day duration prescriptions is not supported by the evidence. Whilst this study accounted for the cost savings from reduced medicine waste associated with 28-day prescription duration, these short term savings were outweighed by additional transaction and drug wastage costs and longer term healthcare costs arising from reduced adherence. However, our results must be considered with due caution as they rely on the evidence suggesting a positive association between prescription length and adherence; the observational nature of the studies means they are at high risk of bias. In order to identify an optimal prescription length, the exact nature of this relationship needs further examination (not least since it is unlikely to be linear nor constant between different populations and disease areas). Hence we suggest implementing different duration prescriptions only within, for example, a stepped-wedge cluster randomised controlled trial design to inform a more rigorous assessment of the costs and/or (short term) health impacts of different duration prescriptions.

Figures

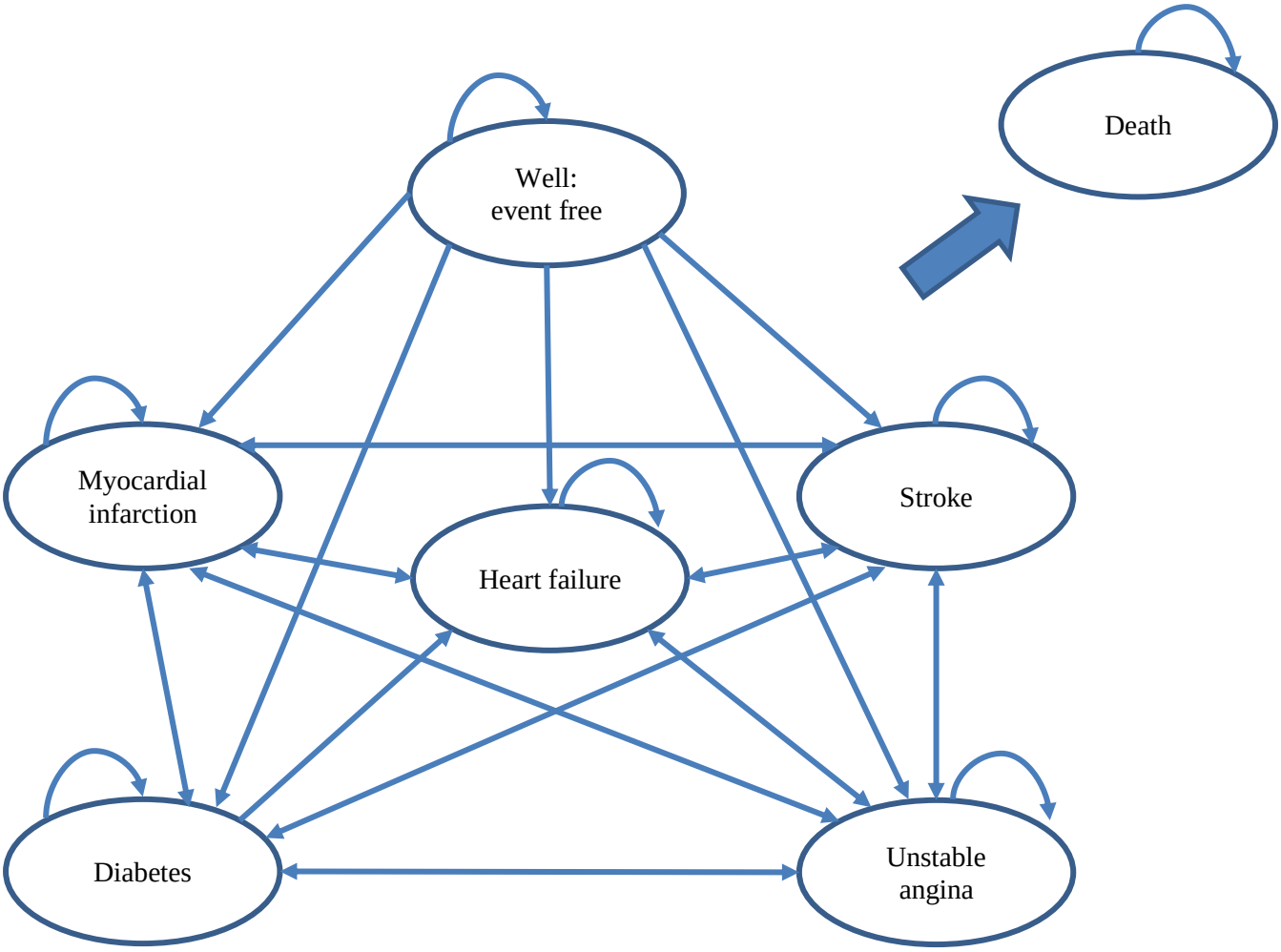
Figure 1: Decision tree to illustrate the general approach to modelling



p = Probability of perfect adherence in active treatment arm of existing model (in this study it is assumed that p=1)

RR=Relative risk of being adherent with a 28-day prescription compared to 3-month prescription.

Figure 2: Schematic representation of the Markov model used in Case Study 1: Antihypertensive medications for prevention of cardiovascular events in patients with essential hypertension



Arrows represent the possible transitions between each of the health states. Diagram based on model description reported in NICE guidance (CG127, updated 2011).[18]

Tables

Table 1: An overview of the methodological approach used in the three case studies

METHODS	
Stage 1	**Appropriate decision models were identified.** These had been used by NICE to assess the cost-effectiveness of relevant medications. The selected models are summarised in Table 2.
Stage 2	**Additional data was identified** (if not already included in the original decision model) as follows: - (i.) the relative treatment effects of treatment versus placebo - (ii.) relationship between adherence and health consequences - (iii.) relationship between prescription length and adherence - (iv.) transaction costs (dispensing fees and prescriber time) - (v.) cost of drug wastage This data is described for each case study in Table 3.
Stage 3	**The decision model was adapted**. Drawing on the data identified in Stage 1, the input parameters and/or model outputs of the identified decision model were adjusted to account for different costs, QALYs and adherence associated with no treatment and treatment with different prescription duration
RESULTS	
Health consequences, costs, ICERs and Incremental net benefit (INB) were reported for: - treatment compared to placebo - treatment with 3-month compared to 28-day prescription duration The results for each case study are reported in Tables 4, 5 and 6.	

Table 2: Key characteristics of the source models

	Case Study 1: Antihypertensive medications for prevention of cardiovascular events in patients with essential hypertension	**Case Study 2: Drugs for prevention of cardiovascular events in patients with type 2 diabetes**	**Case Study 3: Selective serotonin reuptake inhibitors (SSRIs) for depression**
Type of model	Markov model with 6 month cycles and 2,000 iterations	Patient-level simulation model with 12 month cycles and 1,000 iterations	Decision tree
Source of model	NICE clinical guidance (CG127) [18]	The original model is the UKPDS model. It was adapted by NICE for clinical guidance (NG28) [32]	NICE clinical guidance (CG90) [33]
Time horizon	Lifetime	40 years (equivalent to lifetime, given the average starting age was >60 years)	14-15 months (this included a 2-3 month acute treatment phase, a 6 month maintenance treatment phase, and a 6 month follow-up phase)
Comparators	Four groups of alternative anti-hypertensive drugs (ACEIs/ARBs, beta-blockers, calcium-channel blockers, thiazide-type diuretics) and no treatment	The model was run separately for three discrete stages of disease progression (initial therapy, first intensification and second intensification). In each stage at least seven comparators were modelled (e.g., for initial therapy, this included placebo and metformin)	One analysis focused on pharmacological interventions (ten different antidepressants were assessed). Another analysis focused on combination therapy (CBT combined with SSRI treatment compared to SSRI treatment alone)
Selected base-case patient characteristics	65-year old male with essential hypertension (2% cardiovascular disease risk, 1% heart failure risk and 1.1% diabetes risk)	Newly diagnosed patients with type 2 diabetes seeking initial therapy. 57.1% were male and the mean age was 59.8 years	Patients with moderate to severe depression
Perspective	NHS for costs and patients for health outcomes	NHS for costs and patients for health outcomes	NHS for costs and patients for health outcomes
Health outcome	QALYs which reflected prevention of cardiovascular events (non-fatal unstable angina, myocardial infarction, heart failure and stroke, and cardiovascular-related deaths) and side effects (onset of heart failure and diabetes)	QALYs which reflected the impact of treatment on the first occurrence of seven diabetes-related complications (fatal or non-fatal MI, other IHD, stroke, heart failure, amputation, renal failure and eye disease measured in terms of blindness in one eye) and death. All based on data from UKPDS RCT.[34]	QALYs (utility scores were based on a study by Sapin et al. 2004).[35]
Key clinical input parameters	Baseline risks were identified from a range of sources.[18]	Treatment effects on HbA1c, weight, hypoglycaemic episodes and treatment drop outs due to intolerance were taken from a clinical review network meta-analysis) [32]	Odds and probabilities of drop out (after 2-3 months), remission (after 8-9 months) and relapse (after 14-15 months) were identified in a literature review and through expert opinion. (see Appendix Table A3.2)
Discounting	3.5% for costs and QALYs	3.5% for costs and QALYs	3.5% for costs and QALYs
Key limitations of model	No probabilistic sensitivity analyses were reported	No placebo treatment group was included in the first and second intensification of treatment. Patients on initial treatments thus moved to metformin-sulfonylurea (first intensification) then metformin-NPH insulin (second intensification) after a period of time	Treatment continued for only 9 months with follow-up for a further 6 months. Although this model was developed to inform current NICE guidance and is consistent with other SSRI studies (see Cipriani et al. 2009 [36]), this may not reflect current clinical practice and may not capture all costs and outcomes

Table 3: Identified data and key assumptions used in the adapted models

	Case Study 1: **Antihypertensive medications for prevention of cardiovascular events in patients with essential hypertension**	**Case Study 2:** **Drugs for prevention of cardiovascular events in patients with type 2 diabetes**	**Case Study 3:** **Selective serotonin reuptake inhibitors (SSRIs) for depression**
(i.) the relative treatment effects of treatment versus placebo	The source model (NICE CG127), which included a 'No treatment' comparator	The source model (NICE NG28), which included a 'placebo' comparator	A clinical evidence review published alongside NICE CG90 which included evidence on treatment versus placebo
(ii.) Relationship between adherence and health consequences	Assumed to be linear since no relevant evidence was identified		
(iii.) Relationship between prescription length and adherence	Studies by Hermes et al. 2010 (RR=0.92) and Taitel et al. 2012 (RR=0.85)[19, 20] identified in systematic review[13]	Studies by Hermes et al. 2010 (RR=0.891) and Taitel et al. 2012 (RR=0.863)[19, 20] identified in systematic review[13]	Studies by Taitel et al. 2012 (RR=0.748) and Pfeiffer et al. (RR=0.542) [20, 24] identified in systematic review[13]
(iv.) Transaction costs	Data reported in the analysis of UK primary care data [14]		
Dispensing fees	£0.90		
Prescriber time	£3.77 (in 3 month scenario) £3.76 (28 days)	£3.55 (in 3 month scenario) £3.54 (28 days)	£3.18 (in 3 month scenario) £3.23 (28 days)
(v.) Cost of drug wastage	Data reported in the analysis of UK primary care data [14]		
	£0.51 (in 3 month scenario) £0.07 (28 days)	£1.37 (in 3 month scenario) £0.33 (28 days)	£0.43 (in 3 month scenario) £0.21 (28 days)

RR = relative risk of being adherent. Costs are reported in 2015/6 pounds.

Table 4: Results (Case study 1: Antihypertensive medications for prevention of cardiovascular events in patients with essential hypertension)

	Total lifetime cost	Total lifetime QALYs	Net benefit	Incremental analysis			Incremental net benefit
				Costs	QALYs	ICER	
Source model: No intervention and weighted treatment comparators							
No intervention	£5,185	9.57	£188,762	NA	NA	NA	NA
Typical treatment	£4,563	10.16	£201,245	-£622	0.59	-£1,062	£12,483
First approach[1] based on Hermes (RR=0.916)							
28 day	£5,485	10.12	£199,374	NA	NA	NA	NA
90 day	£4,859	10.16	£200,949	-£626	0.05	-£13,373	£1,575
First approach[1] based on Taitel (RR=0.851)							
28 day	£5,543	10.07	£198,485	NA	NA	NA	NA
90 day	£4,859	10.16	£200,949	-£684	0.09	-£7,794	£2,463
Second approach[2] based on Hermes (RR=0.916)							
28 day	£5,488	10.10	£199,297	NA	NA	NA	NA
90 day	£4,859	10.16	£200,949	-£629	0.05	-£12,478	£1,652
Second approach[2] based on Taitel (RR=0.851)							
28 day	£5,549	10.06	£198,378	NA	NA	NA	NA
90 day	£4,859	10.16	£200,949	-£690	0.09	-£7,432	£2,571
SENSITIVITY ANALYSIS							
First approach[1] based on upper-bound of Hermes relative risk estimate (RR=0.928)							
28 day	£5,478	10.11	£199,478	NA	NA	NA	NA
90 day	£4,859	10.16	£200,949	-£619	0.04	-£14,742	£1,470
First approach[1] based on lower-bound of Taitel relative risk estimate (RR=0.846)							
28 day	£5,547	10.07	£198,437	NA	NA	NA	NA
90 day	£4,859	10.16	£200,949	-£687	0.09	-£7,634	£2,512

NA = not applicable, RR = relative risk of being adherent. Costs are reported in 2015/6 pounds.

[1]The first approach involved adapting the cost and QALY outputs of the model to account for different adherence levels.

[2]The second approach involved adjusting model inputs to account for different adherence levels (i.e. the relative treatment effects, versus no treatment, for each health state).

Table 5: Results (Case study 2: Drugs for prevention of cardiovascular events in patients with type 2 diabetes): Mean years on initial treatment, lifetime costs, QALYs and incremental analysis

	Years on initial treatment[1]	Total lifetime cost	The total cost includes			Total lifetime QALYs	Incremental analysis			Incremental net benefit
			UKPDS[2]	Treatment costs	Additional costs[3]		Costs	QALYs	ICER	
Placebo and treatment arms in source model										
Placebo	2.30	£20,722	£14,223	£5,664	NA	8.912	NA	NA	NA	NA
Treatment (Metformin)	3.80	£19,900	£14,155	£5,016	NA	9.033	-£822	0.121	-£6,791	£3,274
28-day and 3-month prescribing - based on Hermes (RR=0.891)										
28 day	3.64	£20,060	£14,163	£5,087	£70	9.02	NA	NA	NA	NA
3 month	3.80	£19,939	£14,155	£5,016	£39	9.033	-£160	0.013	-£9,134	£429
28-day and 3-month prescribing- based on Taitel (RR=0.863)										
28 day	3.59	£20,082	£14,165	£5,105	£69	9.016	NA	NA	NA	NA
3 month	3.80	£19,939	£14,155	£5,016	£39	9.033	-£181	0.017	-£8,613	£518
SENSITIVITY ANALYSIS										
28-day and 3-month prescribing - based on upper-bound of Hermes (RR=0.926)										
28 day	3.64	£20,032	£14,160	£5,063	£71	9.02	NA	NA	NA	NA
3 month	3.80	£19,939	£14,155	£5,016	£39	9.033	-£132	0.009	-£10,396	£312
28-day and 3-month prescribing- based on lower-bound of Taitel (RR=0.851)										
28 day	3.59	£20,091	£14,165	£5,112	£69	9.016	NA	NA	NA	NA
3 month	3.80	£19,939	£14,155	£5,016	£39	9.033	-£192	0.018	-£8,454	£555

NA = not applicable

RR = relative risk

Costs are reported in 2015/6 pounds.

[1] All initial treatments intensified to metformin-sulfonylurea (first intensification) then metformin-NPH insulin (second intensification) after a period of time.

[2] UKPDS: costs incurred within UKPDS Outcomes Model 1 as a result of survival time and long term complications

[3] Additional costs are the sum of transactional (dispensing fees and prescriber time) and drug wastage costs for the period of time the average patient received initial treatment

Table 6: Results (Case study 3: Selective serotonin reuptake inhibitors (SSRIs) for depression): Lifetime costs, QALYs and incremental analysis for patients with moderate and severe depression

	Moderate depression							Severe depression						
	Total costs	Total QALYs	Net benefit	Incremental analysis				Total costs	Total QALYs	Net benefit	Incremental analysis			
				Costs	QALYs	ICER	INB				Costs	QALYs	ICER	INB
Placebo and 'typical treatment' arms[1]														
Placebo	£203,994	61.13	£1,034,838	n/a				£228,470	49.38	£772,283	n/a			
Treatment	£190,779	62.78	£1,081,502	-£13,215	1.65	-£8,006	£46,664	£215,799	51.37	£825,185	-£12,671	1.99	-£6,384	£52,902
28 day and 3 month prescribing scenarios –Based on Taitel (RR=0.748)														
28 day	£222,910	62.36	£1,040,937	n/a				£251,288	50.87	£779,552	n/a			
3 month	£191,966	62.78	£1,080,315	-£30,944	0.42	-£18,749	£39,379	£216,984	51.37	£823,998	-£34,303	0.5	-£17,281	£44,447
28 day and 3 month prescribing scenarios –Based on Pfeiffer (RR=0.542)														
28 day	£226,157	62.02	£1,030,809	n/a				£254,408	50.46	£768,157	n/a			
3 month	£191,966	62.78	£1,080,315	-£ 34,192	0.76	-£ 20,716	£ 49,506	£ 216,984	51.37	£ 823,998	-£ 37,422	0.91	-£ 18,852	£ 55,841
SENSITIVITY ANALYSIS														
28 day and 3 month prescribing scenarios –Based on upper-bound of Taitel relative risk estimate (RR=0.780)														
28 day	£222,408	62.42	£1,042,503	n/a				£ 250,805	50.93	£ 781,315	n/a			
3 month	£191,966	62.78	£1,080,315	-£ 30,443	0.36	-£ 18,444	£ 37,812	£ 216,984	51.37	£ 823,998	-£ 33,820	0.44	-£ 17,038	£ 42,683
28 day and 3 month prescribing scenarios –Based on lower-bound of Pfeiffer relative risk estimate (RR=0.540)														
28 day	£226,191	62.02	£1,030,702	n/a				£ 254,440	50.45	£ 768,037	n/a			
3 month	£191,966	62.78	£1,080,315	-£ 34,225	0.76	-£ 20,736	£ 49,612	£ 216,984	51.37	£ 823,998	-£ 37,455	0.91	-£ 18,869	£ 55,961

The results are reported for a cohort of 100 patients. Costs are reported in 2015/6 pounds.

[1] The 'typical treatment' comparator included a weighted average of the costs associated with ten groups of antidepressant medications based on Prescription Cost Analysis figures published by NHS England which show the total number of items dispensed in the community (the proportions were for 2014, the most recent available data). The proportions calculated were: Citalopram (0.341), Duloxetine (0.034), Escitlopram (0.022), Fluoxetine (0.150), Fluvoxamine (0.001), Mirtazapine (0.146), Paroxetine (0.036), Reboxetine (0.001), Sertraline (0.187), Venlafaxine (0.081).

Acknowledgements:

The authors wish to thank the authors of the decision models for allowing us to use their work in our analysis. The models were originally developed by the NICE internal guideline team and the National Guideline Centre (NGC) (case studies 1 and 2) and the National Collaborating Centre for Mental Health (NCCMH) (case study 3). The authors of this paper are responsible for the adaptations to the decision models.

The authors also wish to thank Jon Sussex (Cambridge Centre for Health Services Research, RAND Europe), Rachel Elliott (University of Manchester) and other colleagues at the Cambridge Centre for Health Services Research (RAND Europe and University of Cambridge) for providing valuable input and advice.

The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR or the Department of Health.

Data Availability Statement:

The decision models used in this study were developed and shared with the authors by third parties (NGC and NCCMH). Whilst not publicly available, they were provided to the journal's peer reviewers for their reference when reviewing this paper and may be requested from the corresponding author [AM].

Author contributions:

All authors contributed to the conception and design of this study. Adam Martin and Edward Wilson led the adaptations of the decision models and the reporting of results. All authors

were involved in drafting and commenting on the paper and have approved the final version. Adam Martin is the guarantor of the study.

Compliance with Ethical Standards' / Funding sources:

Adam Martin, Rupert Payne and Edward Wilson declare that they have no conflict of interest.

This research was supported by a grant from the National Institute for Health Research (NIHR), Health Technology Assessment funding stream (Grant Reference: NIHR HTA 14/159/07).

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