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Title:

Economic evaluation of a behavior-modifying intervention to enhance antiepileptic drug adherence

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Abstract

Between 35% and 50% of patients with epilepsy are reported not to be fully adherent to their medication schedule. We aimed to conduct an economic evaluation of strategies for improving adherence to antiepileptic drugs. Based on the findings of a systematic review, we identified an implementation-intention intervention (specifying when, where and how to act) which was tested in a trial that closely resembled current clinical management of patients with epilepsy, and which measured adherence with an objective and least biased method. Using patient-level data, trial patients were matched to those recruited to the Standard And New Antiepileptic Drugs trial, according to their clinical characteristics and adherence. Generalised linear models were used to adjust cost and utility in order to estimate the incremental cost per quality-adjusted life-year (QALY) gained from the perspective of the National Health Service in the UK. The mean cost of the intervention group, £1,340 (95% CI £1,132, £1,688) was marginally lower than that of the control group representing standard care £1,352 (95% CI £1,132, £1,727). QALYs in the intervention group were higher than the control, 0.75 (95% CI 0.70, 0.79), compared with 0.74 (95% CI 0.68, 0.79), resulting in a cost saving of £12 (€15, US$19) and the intervention being dominant. The probability that the intervention is cost effective at a threshold of £20,000 per QALY is 94%. Our analysis lends support to the cost-effectiveness of a self-directed, implementation-intention intervention for improving adherence to antiepileptic drugs. However, as with any modeling dependent on limited data on efficacy, there is considerable uncertainty surrounding the clinical effectiveness of the intervention which would require a substantive trial for a more definitive conclusion.

Key words

Adherence, economic evaluation, cost-effectiveness analysis, antiepileptic drug

Introduction

Medication adherence is the extent to which patients take their medicines as prescribed, from initiation through to the end of prescribing, in terms of both prescribed dose and dosing interval [1]. Between 35% and 50% of patients are reported not to be fully adherent to their antiepileptic drug (AED) dosing schedules [2,3,4]. These patients are exposed to a higher risk of seizures and an increased time to remission [4]. Low adherence to AEDs may also be associated with increased mortality including sudden unexplained death [5], and hospital admissions [6]. Whilst large cross-sectional studies have demonstrated substantial difference in health outcomes between patients with high and low adherence, prospective studies are lacking. However, current evidence suggests that sub-optimal adherence can lead to reduced quality of life and increased pressure on healthcare budgets.

The causes of non-adherence are multifactorial [7,8,9], and include those that are related to: (i) patients, such as forgetfulness, ambivalence or different beliefs and understanding of the aims of treatment; (ii) healthcare personnel, such as a lack of shared decision-making; (iii) health systems, such as barriers to accessing treatment or information; (iv) socioeconomics, including patients' inability to pay for AEDs; (v) the condition, such as treatment discontinuation upon seizure control; and (vi) treatment, for instance, adverse effects, complexity or frequency of dosing regimen. Non-adherence is often categorised as being intentional or unintentional, with the former potentially influenced by interventions such as use of effective communication to improve patients' motivation, understanding or beliefs [10]. Unintentional non-adherence may be improved by interventions that remind patients when doses are to be taken or by the removing barriers to adherence such as with digital diary reminder alarms or by reducing the regimen frequency [11,12].

A Cochrane review of trials of adherence-enhancing interventions for epilepsy [13] identified behavioural interventions, such as the use of intensive reminders (e.g. prescription refill and appointment-keeping reminders) [14], and 'implementation intention' interventions (where patients note when and where they intend to take their AEDs, and what they would be doing at the moment they will take their medications) [15], to provide more positive effects on adherence than interventions based on education and counselling. However, trials were short in duration, were inadequately powered (or not designed) to detect differences in seizure control, and did not consider the cost-effectiveness of interventions.

Given that interventions to improve adherence require utilisation of healthcare resources, and that the case for the cost-effectiveness of adherence-enhancing interventions in general has not been made [16,17], we aimed to estimate the cost-effectiveness of the most plausibly effective intervention for improving patients' adherence to AEDs.

Methods

Study selection

The Cochrane review noted that the studies included differed widely according to intervention and measures of adherence and combining data in a meta-analysis was not deemed to be appropriate [13]. The review also highlighted methodological limitations increasing the risk of bias, and limitations in reporting that reduce transparency. Five studies were conducted in the United States [14,18-21] and one was conducted in the United Kingdom [15]. Four studies were pre-1990 [14,18-20], and therefore may not adequately reflect current clinical practice, and one considered a sample of only 22 patients [21]. We focussed on the trial that measured adherence with an objective and least biased method and for which we were able to obtain patient-level data to improve the accuracy of the economic evaluation.

This resulted in the selection of a trial, hereafter referred to as the 'Brown' trial [15], which demonstrated that a simple, intention-implementation intervention using self-administered questionnaire, improved adherence compared to control at 1-month (93.4% vs. 79.1% doses taken, $p<0.01$). Eighty-one patients were recruited to the trial from the outpatient clinic at the Royal Hallamshire Hospital, Sheffield, United Kingdom. Eligibility was based on a diagnosis of epilepsy, patients being aged 16 and over who were responsible for their own medicine taking. Only those who were prescribed AEDs which could be dispensed in a monitoring bottle were included. Patients were excluded if they were receiving a diagnosis of epilepsy for the first time, if they were already using an adherence-enhancing intervention, if they were taking AEDs more than twice a day or had learning difficulties [15].

Intervention

The intervention was administered as part of a booklet of self-report measures, after a neurology appointment [15]. Both control and intervention groups completed the booklet, with the booklet for the intervention group containing an extra page corresponding to the intervention. The intervention was designed to automate triggering intended behaviour (medicine taking), based on an "if-then" format ("*If* it is time X in place Y and I am doing Z, *then* I will take my pill dose").

Comment [P1]: The intervention was the III questionnaire not the MEMS bottles. I think we should insert a picture with the III here (with permission we could use the same one we included in the original paper). We can also include a photo of the mems bottles.

Adherence measurement

Patients were supplied their medication in bottles with a Medication Event Monitoring System device (MEMS, MWV Healthcare, Richmond, VA), designed to register the times at which the bottle was opened. Patients completed an additional questionnaire booklet one month after the initial visit to provide follow-up information, and returned their MEMS device.

Economic evaluation

We conducted a cost-utility analysis of the adherence-enhancing intervention for adult patients with epilepsy. Direct medical costs were estimated from the perspective of the National Health Service in

the UK, and health outcomes expressed as quality-adjusted life-years (QALYs) in line with guidance issued by the National Institute for Health and Care Excellence (NICE) [22]. NICE is the statutory body in the UK responsible for providing national guidance and advice to improve health and social care. Core tenets to its decision-making are the consideration of clinical effectiveness and cost-effectiveness, with the latter measured in terms of incremental costs per QALY gained. A modelled extrapolation of trial data to 1 year was performed to reduce time horizon bias and assess the impact of the intervention's durability on cost-effectiveness.

Estimating impact of adherence on health outcomes

The Brown trial measured adherence as the primary outcome but did not measure costs or health outcomes [15]. We therefore estimated the impact of the adherence-enhancing intervention on costs and utilities indirectly by matching patients to those recruited to the Standard And New Antiepileptic Drugs (SANAD) trial [23], for which we had access to patient-level data. Patients in the Brown trial were first matched with SANAD patients according to prescribed AED. In the case where more than one AED matched (e.g. in the context of combined treatment), the primary AED was assigned. In cases where no AED matched, the AED was assigned as 'Other'. In the base-case analysis, patients were matched using propensity scoring, based on age, gender and 12-month remission. As the majority of patients who entered the SANAD trial were treatment naïve, patients from SANAD were matched based on year 1 characteristics to allow the inclusion of remission. The number of missed doses calculated from MEMS data in the Brown trial was mapped onto responses to the adherence question in SANAD, which asked patients "How often, in the past three months, would you say that you have missed taking your antiepileptic medication?" with 4 possible response categories: never, <once a month, between once a week and once a month, and >once a week.

Comment [P2]: The reviewers have asked for more info on the measures. The only measure we cover here seems to be this. Perhaps Tony can add a little about how the questionnaire was administered, what else it asked about and how many items it included.

Costs

Healthcare resource use in the SANAD trial was measured by administering a questionnaire to patients at 1 year, which asked about their use of medications, attendance (or admission) to hospital, investigations received and appointments with health care professionals over a 3 month recall period. Resource use was scaled up to a period of 1 year and combined with AED cost, in line with the original trial-based economic analysis [23,24]. This implicitly captured any resources used to manage adverse reactions. Total costs, based on NHS unit costs, were inflated to 2011 values [25]. A Generalised Linear Model (GLM) (gamma family, log link) was used to adjust total cost for age, gender, remission status and AED. Observations were weighted in the GLM by the number of times they appeared as a nearest neighbour during propensity matching.

The cost of the intervention was based on the time taken to discuss the intervention with the patient. Expert opinion indicated that the intervention would take 10 minutes of a health care professional's time to explain and administer, and that a nurse was the most likely health care professional to administer the intervention. The intervention cost therefore comprised of £17 staff costs [25], plus £0.67 for the cost of providing a single sheet of printed paper. The latter was based on £250 for a printer, conservatively assuming that GP surgeries are not equipped with printing facilities, £15 for a cartridge capable of printing 400 sheets, and £6.50 for the required quantity of paper.

Utilities

SANAD patients' responses to the NEWQoL questionnaire at 1 year follow-up were converted to utilites by applying the tariffs for the NEWQoL-6D epilepsy-specific QALY measure [26]. The EQ-5D has been criticised previously for not reflecting the paroxysmal nature of seizures and epilepsy. Stavem (1998) [27] found little statistical association between the EQ-5D and health state utility measured directly by time trade off and standard gamble methods that more directly measure the impact of epilepsy on patient well-being. The NEWQoL-6D includes domains considered to be of more relevance to epilepsy, namely: worry, depression, memory, concentration, control and stigma.

QALYs were calculated according to the trapezoidal rule for the area under the curve, and adjusting for baseline. In order to calculate health state utilities for patients from the Brown trial, we specified a GLM for *disutility = 1-utility*, (Poisson family, log link), to adjust for age, gender, and baseline remission status and AED. Observations were weighted in the GLM by the number of times they appeared as a neighbour during propensity matching.

Analysis

Coefficients from regression models were applied to the matched subset of patients from the Brown trial, to estimate costs and utilities. Where AEDs from the Brown trial did not match with an AED from SANAD, a mean average of the AED GLM coefficients was used for modelling. No discounting of costs or health utility was applied as the time horizon of the model was set to one year. Cost-effectiveness was assessed according to the incremental cost effectiveness ratio (ICER) for the intervention, calculated as:

$$\mathrm{ICER} = \frac{\mathrm{Cost}_{\mathrm{intervention}} - \mathrm{Cost}_{\mathrm{control}}}{\mathrm{QALY}_{\mathrm{intervention}} - \mathrm{QALY}_{\mathrm{control}}}$$

An intervention with a lower ICER is deemed to be more cost effective than one with a higher ICER. NICE considers an ICER below £20,000 to £30,000 per QALY to mean a health technology represents good value for money for the NHS in the UK [22].

Sensitivity analysis

A univariate sensitivity analysis was conducted to assess the impact of varying the total cost of the intervention (£10 to £100 as a pragmatic, plausible range) on the ICER. Sensitivity analyses based on the 95% confidence intervals of the GLM coefficients were also considered, however these would not make allowance for any correlation between coefficients and therefore a probabilistic sensitivity analysis (PSA), which assessed the simultaneous uncertainty of model parameters, was considered more informative. Correlation between GLM coefficients is reflected in the PSA by use of Cholesky

decomposition upon the covariance matrix. Uncertainty in the cost of the intervention was represented by a gamma distribution on the number of minutes of nurses' time, with an assumed 95%CI of (5, 15 minutes). PSA was accomplished by drawing iteratively (10,000 times) from the generated distributions. A cost effectiveness acceptability curve (CEAC) was constructed to depict the probability of the intervention being cost-effective for a given cost-effectiveness threshold [28].

Scenario analyses

The model was analysed with a healthcare professional cost of £27, to represent 10 minutes of the time of a consultant who might alternatively administer the intervention [25]. A further analysis calculated QALYs from UK tariffs applied to EQ-5D responses at 1 year follow-up. The assumption that the effect of the intervention would be maintained for the full year was tested in alternative scenarios, whereby i) adherence was assumed to reduce immediately to the level of the control group after 1 month (duration of the Brown trial); and ii) where the adherence benefit tapered in a linear manner, to that of the control group over a 3-month period.

The effects of alternative approaches for matching were explored by firstly including AED in the propensity scoring, and secondly by implementing an exact distance method of matching patients according to their age (within 5 years), gender, 12-month remission and AED.

The economic evaluation was analysed in Microsoft Excel 2010 and reported according to the Consolidated Health Economic Evaluation Reporting Standards [29].

Results

Patients

In the base case, all 72 patients from the Brown trial were matched with 224 (of 739 patients for whom demographic and either cost or NEWQoL data were available) from SANAD. The baseline demographic and clinical characteristics are presented in Table 1.

Inert Table 1 here

The results of mapping of patients within each adherence category in the Brown trial to those in the SANAD trial are presented in Table 2. It is noted that SANAD participants have a higher percentage of patients who self-report to be 100% adherent.

Insert Table 2 here

Base case analysis

The GLM coefficients for costs and disutilities are presented in Table 3. Patients in remission generate significantly lower costs than those whose seizures are uncontrolled. Treatment costs associated with females are lower than those associated with males, and costs increase with age. The base-case AED, carbamazepine, was the least expensive overall, followed by topiramate, oxcarbazepine, lamotrigine and then gabapentin. The relationship between cost and adherence is not monotonic; highest costs are seen for the least adherent patients, followed by the most adherent patients, then those who miss at least one dose per month, but less than one dose per week. Patients who miss less than one dose per month are associated with the lowest cost. Patients in remission had higher utility than those experiencing uncontrolled seizures. Utility appears lowest for carbamazepine, followed by lamotrigine, gabapentin, topiramate, then oxcarbazepine. Whilst patients who miss less than one dose per month, or at least one dose per month but less that one per week, have marginally higher utility than those who miss no doses, lowest adherence is associated with a negative effect on utility.

The mean cost of the intervention group, £1,340 (95% CI £1,132, £1,688) is lower than that of the control group £1,352 (95% CI £1,132, £1,727) resulting in a cost saving of £12 (95% CI -£96, £61), or

£1,158 per 100 patients. QALYs in the intervention group were 0.75 (95% CI 0.70, 0.79) compared with 0.74 (95% CI 0.68, 0.79) in the control group, a difference of 0.01 (95% CI 0.00, 0.03). As the intervention is both less costly and more effective, it dominates the control strategy.

Insert Table 3 here

Sensitivity and scenario analyses

A univariate sensitivity analysis of the cost of the intervention resulted in ICERs ranging from the intervention being dominant when the cost was £10, to £5,915 per QALY gained when the cost was £100. Cost effectiveness estimates were stable to univariate sensitivity analyses on the GLM coefficients. The PSA indicated that 56% of simulations were in the south-east quadrant of the cost-effectiveness plane (dominant) while 37% of simulations suggested that the intervention was both more costly and more effective (Figure 1). Less than 6% of simulations showed the intervention to be less effective. The probabilities of the intervention being cost-effective at ceiling ratios of £20,000 and £30,000 per QALY were 94% and 95%, respectively (Figure 2).

Insert Figures 1 and 2 here

In a scenario where the intervention is delivered by a consultant rather than a nurse, the intervention remains dominant, with a mean cost of £1,350. A scenario in which adherence in the intervention group tapers to that of control group between months 1 and 4 produces an ICER of £4,645 per QALY gained, while a scenario of the intervention having no effect on adherence after 1 month increases the ICER to £15,281 per QALY gained. When EQ-5D was used as a utility measure, QALYs in the intervention group are 0.68 (95% CI 0.55, 0.75), compared to 0.66 (95% CI 0.52, 0.73) in the control group; the incremental QALY of 0.02 (95% CI -0.01, 0.05), indicating that the intervention dominates. When AED was included in propensity score matching, the incremental cost of £338 (95% CI £260, £424) and QALY of 0.03 (95% CI -0.01, 0.06) resulted in an ICER of £13,361 per QALY. The alternative method of matching by age, gender, remission and AED resulted in an incremental

cost of £125 (95% CI £-115, £306), a QALY gain of 0.02 (95% CI 0.01, 0.04) and an ICER of £5,121 per QALY gained.

Discussion

Our economic evaluation suggests that a simple intervention which encourages patients to make explicit their intentions to take their antiepileptic medications can represent a cost-effective use of NHS resources, being both less costly and more effective and a 95% probability of being cost effective. Considering different modelling assumptions, the ICER remains well within the NICE threshold of £20,000 to £30,000 per QALY.

The analysis revealed that the associations between adherence, and cost and health state utility are not monotonic, with the highest costs and lowest health state utility observed for the least, and then most adherent patients. We hypothesise that patients who are most adherent to their medication may also engage more closely with the healthcare system in general; thus generating more visits to specialists and associated costs. Conversely, patients with poorly controlled tonic clonic seizures may be more adherent, but consume higher healthcare resources due to their refractory epilepsy. Least adherent patients may generate increased costs through increased seizure frequency, seizure severity and seizure-related injuries. Cross-sectional studies have indicated that low adherence is associated with lifestyle choices such as drinking and smoking, and is also more prevalent in patients with mental health problems and general poor health, these factors are not directly associated with epilepsy, but impact upon quality of life and resource use. We also note that perceived improvements in health, such as good seizure control can be a risk factor for non-adherence. A prospective study would be required to further explore these potential confounding factors.

This study is the first economic evaluation of any adherence-enhancing intervention in epilepsy, and has strengths in that it utilitises patient-level data from randomised controlled trials and addresses many of the methodological limitations of comparable evaluations in other clinical contexts [16,17].

Our study benfits from having the intervention's efficacy established using an objective and reliable measure of adherence [30]. Cost and utility decrement models were generated as generalised linear models, accounting for relevant covariates and the positively skewed nature of the data [31]. Correlations among covariates were conserved for the probabilistic sensitivity analysis.

Our analysis necessitated a number of important assumptions owing to the short follow up period and a lack of data on health outcomes and costs in the Brown trial. Consequently, our reliance on matching patients to the SANAD trial resulted in near, but imperfectly matched populations. For instance, the majority of SANAD patients (82%) had only 1 year of treatment experience at the point of analysis, whilst the Brown trial focussed on chronic cases (mean of 19.5 years duration of seizures). There is conflicting evidence as to whether duration of treatment experience has a negative impact on adherence (Cramer et al, 2002) or is a neutral factor (Sweileh et al, 2011; Ferrari et al, 2013). There is also evidence that uncontrolled seizures is associated with non-adherence (Ferrari et al, 2013) though one study found erratic adherence with over consumption of AED was more prevalent (Carpentier, 2013) in refractory epilepsy. We also acknowledge the differences in the methods of adherence measurement in the SANAD and Brown studies. Comparison between the two data sets suggests that a lower proportion of patients report low adherence when assessed by questionniare, in agreement with literature on the topic [32]. There is also very little evidence linking adherence to AEDs directly with seizure count [2], meaning that our analyses may be susceptible to bias; though recent seizure experience is linked to higher AED adherence (Ferrari et al, 2013). This may have been further affected by our extrapolation of 1-month data to a period of a year. However, with respect to behavior modification, there is evidence of sustainable effects on outcomes with comparable interventions targeting smoking cessation [33], blood donation [34] and oral contraceptive use [35].

Notwithstanding these limitations, the results remained well within the cost-effectiveness threshold when uncertainty was explored in sensitivity analyses. Comparing best-worst scenarios the ICER

remained below £30,000 per QALY gained and probabilistic sensitivity analysis showed a very high probability of the intervention being cost-effective.

Based on the results of our evaluation, our analysis lends support to the cost-effectiveness of a self-directed, implementation-intention intervention (III) for improving adherence to antiepileptic drugs in the context of the NHS in the UK. The low cost of the intervention and likely ease of widespread implementation makes it an appealing method to improve health outcomes in epilepsy. However, as with any modeling dependent on limited data on efficacy, there is considerable uncertainty surrounding the clinical effectiveness of the intervention which would require a more substantive trial for a more definitive conclusion. What is more, the patients included in the Brown trial all had established epilepsy and were taking AEDs prior to the study. Whilst there is no psychological reason why an implementation intention intervention should not be effective when AEDs are first started (and indeed it may, theoretically, be more effective in this setting), future studies would have to examine the effects of an III in the first treatment scenario.

In the past 20-30 years there has been a significant investment in the development of new medicines for epilespy. Whilst these new AEDs have increased prescribers' choice, there is no evidence that they have had any impact on the porportion of people with refractory epilepsy. Given the treatment gap in epilespsy as well as significant problems with adherence, it is important that there is adequate assessment of inverventions to improve adherence, which offer an opportunity to improve quality of life in a cost effective way. The Brown study has demonstrated the positive effect of an III on tablet taking behaviour in patients with epilepsy. This study suggests that the intervention may be cost-effective. An appropriately powered future study will need to demonstrate whether improved AED use is associated with improvements in health and social outcomes and patients' quality of life.

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Figure legends:

Figure 1. Plot of 10,000 probabilistic sensitivity analysis simulations on the cost effectiveness plane

Figure 2. Cost-effectiveness acceptability curve for the base-case analysis