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

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## A R T I C L E   I N F O

## A B S T R A C T

Between 35% and 50% of patients with epilepsy are reported to be not 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 with those recruited for the Standard and New Antiepileptic Drugs trial according to their clinical characteristics and adherence. Generalized 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, £1340 (95% CI: £1132, £1688), was marginally lower than that of the control group representing standard care, £1352 (95% CI: £1132, £1727). Quality-adjusted life-year values in the intervention group were higher than those in the control group, i.e., 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 with 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.

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## 1. Introduction

Medication adherence is the extent to which patients take their medicines as prescribed, i.e., from the 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 to be not fully adherent to their antiepileptic drug (AED) dosing schedules [2–4]. 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 with increased hospital admission rates [6]. While large cross-sectional studies have demonstrated substantial difference in health outcomes between patients with high adherence and patients with low adherence, prospective studies are lacking. However, current evidence suggests that suboptimal adherence can lead to reduced quality of life and increased pressure on health-care budgets.

The causes of nonadherence are multifactorial [7–9] and include those that are related to the following: (i) patients, such as forgetfulness, ambivalence or different beliefs and understanding of the aims of treatment; (ii) health-care 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. Nonadherence is often categorized as being intentional or unintentional, with the former being potentially influenced by interventions such as the use of effective communication to improve patients' motivation, understanding, or beliefs [10]. Unintentional nonadherence may be improved by interventions that remind patients when doses are to be taken, by 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 behavioral interventions, such as the use of intensive reminders (e.g., prescription refill and appointment-keeping reminders) [14], and 'implementation intention' interventions

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(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 counseling. 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 utilization of health-care 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.

## 2. Methods

### 2.1. 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 reduced transparency. Five studies were conducted in the United States [14,18–21], and one was conducted in the United Kingdom [15]. Four studies were conducted 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 a self-administered questionnaire, improved adherence compared with control at 1 month (93.4% vs. 79.1% doses taken, p < 0.01). Eighty-one patients were recruited for the trial from the outpatient clinic at the Royal Hallamshire Hospital, Sheffield, United Kingdom. Eligibility was based on a diagnosis of epilepsy, with patients being 16 years of age 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 if they had learning difficulties [15].

### 2.2. 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 worksheet (Fig. 1). The intervention was designed to automate triggering-intended behavior (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").

### 2.3. Adherence measurement

Patients were supplied with their medication in bottles with a Medication Event Monitoring System device (MEMS, MWV Healthcare, Richmond, VA). Medication Event Monitoring System devices contain microcircuits in the caps of medication bottles, which register the times of bottle openings [22]. Patients completed an additional questionnaire booklet one month after the initial visit to provide follow-up information and returned their MEMS device.

### 2.4. 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 were expressed as quality-adjusted life-years (QALYs) in line with the guidance issued by the National Institute for Health and Care Excellence (NICE) [23]. The National Institute for Health and Care Excellence 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 being measured in terms of incremental costs per QALY gained. A modeled extrapolation of trial data to 1 year was performed to reduce time horizon bias and to assess the impact of the intervention's durability on cost-effectiveness.

### 2.5. 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 indirect impact of the adherence-enhancing intervention on costs and utilities by matching patients with those recruited for the Standard and New Antiepileptic Drugs (SANAD) trial [24], for which we had access to patient-level data. Patients in the Brown trial were first matched with SANAD patients according to prescribed AEDs. 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, less than once a month, between once a week and once a month, and more than once a week. This question was one of 45 in the questionnaire that patients were asked to complete and return in a prepaid envelope after 1-year participation in SANAD [25].

### 2.6. Costs

Health-care 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 the 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 [24,25]. This implicitly captured any resources used to manage adverse reactions. Total costs, based on NHS unit costs, were inflated to 2011 values [26]. A generalized linear model (GLM) (gamma family and 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 neighbor 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 expert opinion indicated that the intervention would most likely be delivered by a nurse, and take 10 minutes to explain and administer the intervention. The intervention cost, therefore, comprised £17 staff costs [26] 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