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Enhancing antiepileptic drug adherence: A randomized controlled trial

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ABSTRACT

Suboptimal adherence to antiepileptic drug (AED) treatment is commonplace, and increases the risk of status epilepticus and sudden unexplained death in epilepsy. This randomized controlled trial was designed to demonstrate whether an implementation intention intervention involving the completion of a simple self-administered questionnaire linking the intention of taking medication with a particular time, place, and other activity can improve AED treatment schedule adherence. Of the 81 patients with epilepsy who were randomized, 69 completed a 1-month monitoring period with an objective measure of tablet taking (electronic registration of pill bottle openings, Medication Event Monitoring System [MEMS]). Intervention participants showed improved adherence relative to controls on all three outcomes: doses taken in total (93.4% vs. 79.1%), days on which correct dose was taken (88.7% vs. 65.3%), and doses taken on schedule (78.8% vs. 55.3%) ($P < 0.01$). The implementation intention intervention may be an easy-to-administer and effective means of promoting AED adherence.

1. Introduction

Approximately 60% of patients with epilepsy achieve full control of their seizures with antiepileptic drugs (AEDs) [1]. Modern medical treatment aims not only to prevent seizures but also to avoid negative effects on cognitive function and emotional, physical, and general well-being. People with epilepsy are most likely to achieve these aims by the regular ingestion of the lowest dose of medication and the smallest number of AEDs necessary [2]. This, in turn, depends on their taking their medication as prescribed. However, research indicates that 30% to 50% of adults with epilepsy adhere poorly to their AED treatment schedules [3]. Adherence problems may be more common in epilepsy than in other medical conditions [4]. Indeed, nonadherence has been identified as one of the most important causes of treatment failure in patients with epilepsy [5],

It is possible that neurologists underestimate the extent of adherence problems in their own clinical practice because patients do not admit failing to take their medication regularly to their doctor [6–8]. Seventy percent of patients with epilepsy state that they never miss a dose [9,10], and the majority of patients admit to missing only one or two doses per month [7]. However, studies using objective measures have revealed much higher rates of irregular AED use. For instance, a study of 33,658 Medicaid recipients showed that less than 80% of the AEDs required for full prescription adherence were picked up by participants in 26% of quarters during the observation period [11]. Two studies using the Medical Events Monitoring System (MEMS)—a pill bottle with an electronic cap that registers each occasion the bottle is opened—found that only 76% of doses were taken overall [12], and that 48% of patients took one-third or fewer of the prescribed AED doses [6]. AED blood levels in the "therapeutic range" can offer false reassurance: although complete nonadherence can be detected using AED blood levels, there is no reliable correlation between the variability of AED blood levels and irregular medication intake [12].

Poor adherence has been shown to affect important treatment outcomes: in the large Medicaid study mentioned above, the numbers of hospital admissions, inpatient treatment days, and emergency room visits were higher in "noncompliant" quarters, resulting in increased total health care spending [11]. Another recent study based on more than 10,000 individuals with epilepsy found that 39% picked up less than 80% of the medication required to cover their AED prescription and that hospital admission rates and health care costs were higher in the nonadherent group [13]. Other studies have shown that patients who miss doses may experience additional seizures [7,14], and may be slower to achieve full seizure control [15]. Lack of adherence to AED treatment has been identified as a potential precipitating cause in 31% of epileptic seizures for which ambulances were called and 13% of seizures requiring emergency hospital admission [16,17]. Patients whose medication intake is irregular are also at increased risk of sudden unexplained death in epilepsy (SUDEP) [18]. After demographic and clinical covariates in the Medicaid study were controlled for,

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the mortality risk in nonadherent patients was more than three times higher than that of adherent patients [11].

For these reasons, interventions that can improve AED treatment adherence are of great clinical interest. Previous studies have tested the effectiveness of a range of strategies including the simplification of AED regimens to no more than two doses per day [12], discussion of serum level measurements with patients [19], and shorter intervals between clinic visits [20]. The most intensive intervention (incorporating counseling, medication containers, self-monitoring, and mailed reminders for prescriptions and appointments) improved adherence in the treatment group and halved seizure frequency [14]. However, this sort of intensive support may not be practical (especially for patients who also miss clinic appointments) or easy to integrate into routine clinical practice.

This study tests whether a simple and self-administered worksheet consisting of an implementation intention intervention (III) can increase AED adherence [21,22]. In this III, patients are asked to write down exactly when and where they will take their medication, using the format of an if–then plan ("*If* it is time X in place Y and I am doing Z, *then* I will take my pill dose"). IIIs target the problem that holding a strong goal intention ("I intend to take my tablets regularly") does not guarantee goal achievement, because people may fail to deal effectively with self-regulatory problems during goal striving. Evidence indicates that the act of writing down an if–then plan can help to "automate" triggering of the intended behavior by sensitizing people to the cues they have written down [23]. This means that they become more likely to complete the intended activity when these cues are encountered [21]. IIIs reduce the burden of having to think about and remember when to act by using environmental cues to trigger the desired behavior. IIIs are not merely a theoretical construct, but have already been proven effective in promoting a range of health behaviors in other areas of medicine including cancer screening, physical activity, and psychotherapy attendance [21].

2. Methods

2.1. Participants

Five consultant neurologists recruited patients consecutively from their outpatient clinic at the Royal Hallamshire Hospital in Sheffield, United Kingdom, between January and June 2007. All patients had a clinical diagnosis of epilepsy, were taking antiepileptic drugs once or twice daily, and were attending the neurology clinic for a follow-up visit. The diagnoses had been made by a consultant neurologist on the basis of clinical history and neurological examination. Neuroimaging, EEG, or video/EEG telemetry had been carried out if clinically indicated. Patients were included only if they were: taking at least one of the AEDs that could be dispensed in the monitoring bottle once or twice daily (carbamazapine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, or zonisamide); at least 16 years of age; able to read and write English; and responsible for taking their own medication. Patients were excluded if they indicated that they were already using a method of ensuring adherence that could be compromised if they took part in the study (e.g., weekly tablet dispensers), if they were receiving a diagnosis of epilepsy for the first time, or if they had learning difficulties. The study was approved by the North Sheffield Ethics Review Committee, and all patients gave written informed consent.

2.2. Study design

We randomized patients to the intervention or control group using a computerized random number generator (http://www.randomizer.org). All patients completed a 14-page packet of self-report measures after they had seen the neurologist (baseline).

The intervention consisted of one additional intention implementation worksheet (up to six items on two pages depending on daily dose) which was included in the questionnaire packet that patients randomized to the intervention were asked to complete (i.e., patients in this group completed a total of 15 pages of questionnaires rather than 14). This additional worksheet is shown in Fig. 1.

Neither the neurologist nor the clinic or pharmacy staff were aware of the patient's group allocation. Following the procedure described by Gollwitzer and Sheeran [21], the III asked participants to specify environmental cues for tablet taking using the format of an "if–then" plan (i.e., participants wrote down exactly when and where they were intending to take their antiepileptic medication every day, and what they would be doing at the moment they would take their AEDs).

All patients picked up a 1-month supply of one of their antiepileptic drugs in an electronic pill-monitoring bottle, which recorded the number and timing of bottle openings (MEMS Aardex Ltd., Switzerland). The electronic monitoring caps can be connected to a personal computer that reads the data from the pill caps' microprocessor and generates a printout of the patient's bottle openings.

One month after the initial clinic visit (follow-up), we approached patients by letter and asked them to complete an additional set of questionnaires and return the electronic pill-monitoring device. In line with previous studies using this method of monitoring, we measured adherence using three different outcome measures counting each opening as a presumptive dose [12]: percentage of doses taken, percentage of days on which the correct number of doses was taken, and percentage of doses taken on schedule. We designated doses as having been taken on schedule if the MEMS bottle was opened within a ±3-hour target time window for each dose.

2.3. Self-report measures

We administered self-report measures to ensure the equivalence of control and experimental groups and to identify factors that could moderate the impact of the III. At baseline, participants completed the following measures: Theory of Planned Behaviour (TPB, 24 items, five scales), Brief Illness Perception Questionnaire (BIPQ, 9 items) [24], Multiple Ability Self-Report Questionnaire (MASQ, 38 items, five scales) [25], Hospital Anxiety and Depression Scale (HADS, 14 items, two scales) [26], Liverpool Seizure Severity Scale (LSSS, 12 items, one scale) [27,28], and a single-item self-estimate of the number of missed doses during the preceding month. At follow-up, participants completed the HADS, LSSS, and Prospective and Retrospective Memory Questionnaire (PRMQ, 7 items, one scale) [29].

2.4. Statistical analysis

We conducted an analysis of variance (ANOVA) on the continuous, cognitive, clinical, and demographic variables measured at baseline to ensure the equivalence of (1) participants who completed both baseline and follow-up measures and participants who completed the baseline measures only (representativeness check), and (2) participants in the intervention and control groups (randomization check). We used χ^2 tests to compare the respective groups on categorical variables. We used an ANOVA to determine the effect of intervention on the three measures of AED adherence.

Because adherence is measured using continuous (0–100%) scales, moderated regression analysis is the appropriate test for identifying possible interactions between condition (intervention