ORIGINAL ARTICLE

Improving Adherence to Medication in Stroke Survivors: A Pilot Randomised Controlled Trial

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Abstract

Background Adherence to preventive medication is often poor, and current interventions have had limited success.
Purpose This study was conducted to pilot a randomised controlled trial aimed at increasing adherence to preventive medication in stroke survivors using a brief, personalised intervention.
Methods Sixty-two stroke survivors were randomly allocated to either a two-session intervention aimed at increasing adherence via (a) introducing a plan linked to environmental cues (implementation intentions) to help establish a better medication-taking routine (habit) and (b) eliciting and modifying any mistaken patient beliefs regarding medication/stroke or a control group. Primary outcome was adherence to antihypertensive medication measured objectively over 3 months using an electronic pill bottle.
Results Fifty-eight people used the pill bottle and were analysed as allocated; 54 completed treatment. The intervention resulted in 10 % more doses taken on schedule (intervention, 97 %; control, 87 %; 95 % CI for difference (0.2, 16.2); $p=0.048$).
Conclusions A simple, brief intervention increased medication adherence in stroke survivors, over and above any effect of increased patient contact or mere measurement. (http://controlled-trials.com, number ISRCTN38274953.)

Keywords Stroke · Adherence · Medication beliefs · Implementation intentions · Antihypertensives

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Introduction

It is estimated that, in developed countries, only 50 % of patients who suffer from chronic diseases adheres to treatment recommendations [1]. Adherence is lower in chronic conditions than in acute conditions and drops off dramatically after the first 6 months of treatment [2]. A recent large-scale survey of over 31,000 patients with hypertension in Italy found that only 41 % had >80 % adherence (measured by dispensed medications) 2–3 years after they were first prescribed, and poor adherence was associated with higher incidence of myocardial infarction, stroke and all-cause death [3].

The current Cochrane review of interventions to improve medication adherence concluded that 'Current methods of improving adherence for chronic health problems are mostly complex and not very effective, so that the full benefits of treatment cannot be realized. High priority should be given to fundamental and applied research concerning innovations to assist patients to follow medication prescriptions for long-term medical disorders' [4, p. 2].

This pilot study aimed to evaluate a brief intervention to increase medication adherence in the secondary prevention of stroke. Stroke is one of the most common causes of death in the USA and UK and is the most common cause of severe physical disability amongst adults. The risk of a recurrent stroke is 30–43 % within 5 years. Guidelines for secondary prevention after ischaemic stroke now recommend antiplatelet therapy and reduction of both blood pressure (BP) and cholesterol level as

key components in reducing the risk of future vascular events [5]. Despite this, adherence to prescribed medication in stroke patients is often suboptimal. For instance, a recent US study of 2,888 stroke patients found that 25 % had discontinued one or more of their medicines at just 3 months post-discharge [6].

Poor adherence may be both non-intentional and intentional. Non-intentional non-adherence (e.g. forgetting) is often a consequence of cognitive impairment [7]. After a stroke, the impact of cerebrovascular disease on cognitive function, particularly memory, may mitigate against adherence, particularly if the patient is elderly and the drug regime is complicated [8].

Brief and easy-to-complete implementation intentions interventions have been shown to be effective at reducing forgetting and improving medication adherence [9]. These involve patients writing 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', e.g. first cup of tea at breakfast in the kitchen cues taking morning medication). If–then planning makes people highly sensitive to written environmental cues, establishes a habit and removes the burden of having to think about and remember when to act by reducing the load on prospective memory as habitual responses become established. Brown and colleagues showed that such an approach was successful in improving adherence in a randomised controlled trial (RCT) in patients with epilepsy (e.g. doses taken on schedule, 78.8 % in the intervention group versus 55.3 % in the control group, $p < 0.01$) [10].

Intentional non-adherence occurs when a patient deliberately chooses not to take their medication, against medical advice. This often depends on the patient's beliefs concerning their condition and/or their medication. Leventhal's self-regulation theory posits that patients have a common-sense model of their illness in terms of beliefs regarding how long it will last, whether it is acute or chronic, and so forth [11]. Patients also have beliefs about treatment, particularly the perceived necessity of medication versus concerns about any possible harmful effects [12]. A recent study in stroke patients found that patients' concerns about their medication (e.g. dependence, toxicity, too many tablets) were key determinants of poor adherence, supporting the self-regulation theory [13].

We report the results of a pilot randomised trial of a brief intervention based on this theoretical framework. Our aim was to increase medication adherence via (a) developing an implementation intentions plan to reduce non-intentional non-adherence and (b) eliciting and modifying erroneous beliefs about medication and stroke to reduce intentional non-adherence. Although we were interested in patients' experiences regarding all of their stroke medication, antihypertensive medication was targeted for measurement, as poor adherence to antihypertensives has been associated with significantly increased risk of stroke and death [14],

and only 30–50 % of patients regularly take their antihypertensive drugs as prescribed [15].

Methods

Participants

In accordance with our published protocol [16], participants were recruited from consecutive discharges from the stroke clinic and stroke unit at the Western General Hospital in Edinburgh between January 2010 and October 2011. Inclusion criteria were first stroke or transient ischaemic attack (TIA), discharged to home and on any preventive stroke medication. All participants gave informed consent for the study which was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975 (revised 2000) and had ethical approval from the South East Scotland Research Ethics Committee (REC ref. no. 09/S1102/36). The study is registered with Current Controlled Trials, http://controlled-trials.com, with the unique identifier number ISRCTN38274953.

Measures

Medication Events Monitoring System (MEMS® Aardex Ltd., Switzerland)

Our primary outcome measure was electronically recorded openings using MEMS pill bottles for 3 months. MEMS pill bottles were used in both treatment arms as MEMS measurement is not immune from the Hawthorne (or mere measurement) effect [17]. Following Brown and colleagues [10], we calculated the percentage of (a) prescribed doses taken, (b) days on which the correct dose was taken and (c) doses taken on schedule, i.e. within a 3-h window of the median time taken. We considered the latter as particularly important, as the implementation intentions intervention aims to establish regular behaviour patterns tied in to a specific time. Median rather than mean time was used to reduce the effect of any outliers.

The Medication Adherence Report Scale (MARS) [18]

The MARS consists of five items relating to taking medication, each scored from 1 to 5 and totalled to give an overall MARS score. The MARS is worded in order to make missing medication seem a normal behaviour, with the aim of reducing social desirability and eliciting honest responses. As the MARS was initially used to detect less than maximum adherence on patients' antihypertensive medicine, patients were asked to answer each question for how they took their 'blood pressure medicines'. The MARS has

been used extensively to measure adherence in patients with chronic diseases and has shown good reliability (internal and test–retest) and validity (convergent and criterion).

Patient Beliefs About Medication and Illness

The Beliefs about Medication Questionnaire (BMQ) [19] was used to assess cognitive representations of medication. We only used the specific subscales (BMQ-specific) which relate to a patient's prescribed medication, as the BMQ-general scales (medication in general) were not associated with adherence in our previous study [13]. The BMQ-specific has two five-item subscales representing (a) beliefs about the necessity of medication (necessity) and (b) concerns/beliefs about the risks and/or negative effects of taking medication (concerns). Patients were asked to give their personal views on the 'medicines prescribed for your stroke or TIA (mini-stroke)'. The BMQ-specific subscales have shown good reliability and validity amongst patients with varied illnesses including heart conditions, asthma and diabetes [19].

Participants were also asked to indicate their perception of the benefits (0–100 %) provided by their stroke medication over the next 5 years following [20] and our previous study [13]. Finally, the Brief Illness Perception Questionnaire (BIPQ) [21] was used to assess patients' views of their illness (i.e. stroke/TIA). The nine-item BIPQ provides an easy-to-complete, psychometrically robust measure of the major components of illness perceptions.

Frenchay Aphasia Screening Test [22]

This screening test, which is frequently used with stroke patients, was developed as a quick and simple method to identify the presence of language disturbance. It has shown good test–retest and inter-rater reliability as well as good construct and criterion validity [22]. In order to ensure that patients would be able to complete all self-report measures, those scoring <13 were excluded from the intervention.

Mini-Mental State Examination (MMSE) [23]

The MMSE is a brief, valid and reliable assessment of various components of cognitive function, which has been widely used in stroke research. We excluded patients scoring <23 from the intervention, as this could indicate cognitive difficulties which could affect study participation.

Procedures

The study was conducted in two stages: In part 1, participants completed a questionnaire, which was used to screen for eligibility for part 2, the pilot randomised trial. All

participants gave separate written informed consent for parts 1 and 2. Full details of the procedures can be obtained from the study protocol [16].

Part 1: Screening for Intervention

Patients consenting to part 1 were sent the MARS, BMQ, BIPQ and perception of benefits questionnaires around 3 months after discharge. They were also asked to list all current medications taken and provide information on any help they currently received in remembering to take their pills.

All patients who reported less than maximum adherence (i.e. MARS scores <25) were considered for the brief intervention (part 2). Those indicating they were not responsible for their own medication, not on any antihypertensive medication or already using pharmacy-supplied Dosette boxes were excluded. Patients eligible for part 2 were sent an invitation letter plus information sheet, consent form and stamped addressed envelope. A power calculation indicated that a sample size of $n=30$ in each treatment arm would detect a medium effect of the intervention on MEMS adherence [16].

Part 2: Intervention Versus Control

Two brief sessions, 2 weeks apart, were conducted by a trained research fellow for both the intervention and control groups, either in the patient's home or at the hospital-based Wellcome Trust Clinical Research Facility. All interviews were timed, digitally audio-recorded and transcribed for a check on treatment fidelity.

All patients were screened (at session 1) using the MMSE and the Frenchay Aphasia Screening Test; there were no exclusions on either test. Patients in both treatment arms were told that we were using the MEMS containers to collect information about how patients took their medication.

Intervention Condition Session 1 focussed on helping each patient establish a better medication-taking routine using an implementation intentions approach to develop an individually tailored coping plan [24]. The plan was introduced at session 1 so that patients could try it out over the 2-week period prior to review in session 2.

Following Brown et al. [10], patients were advised that it was a good idea to make taking their medicines part of a routine and were asked to make a plan to take their tablet(s) at the same time as something else that they did every day. They were then asked to write down the time, place and what they would be doing at the time they would take the first dose of their antihypertensive medicine (i.e. that which would be put in the MEMS pill bottle) on an individualised worksheet (see Fig. 1). This was repeated for all daily doses

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┌─────────────────────────────────────────────────┐
│   ┌─────────────────────────────────────────┐    │
│   │            JOHN'S PLAN                   │    │
│   │  If it is:     7am                       │    │
│   │  And I am:     in the bathroom           │    │
│   │  And I:        am going to clean my teeth│    │
│   │  Then:         I will take my blood      │    │
│   │                pressure tablet           │    │
│   └─────────────────────────────────────────┘    │
│                                                   │
│   ┌─────────────────────────────────────────┐    │
│   │            MARY'S PLAN                   │    │
│   │  If it is:     first thing in the morning│    │
│   │  And I am:     in the kitchen            │    │
│   │  And I:        am making my cup of tea   │    │
│   │  Then:         I will take my tablets    │    │
│   └─────────────────────────────────────────┘    │
│                                                   │
│   Note: 'John' took one anti-hypertensive a day;  │
│   'Mary' was on multiple medications, she took    │
│   them all together in the morning                │
└─────────────────────────────────────────────────┘
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Fig. 1 Examples of implementation intentions plans (following Brown et al. [10])

of this medication. Patients were then asked to repeat each plan up to three times, until they felt they were able to remember it without looking at what they had written down.

The research fellow also took baseline BP readings using an OMRON M10-IT BP monitor, according to a standard protocol. A single reading was taken from each arm; then, the arm with the highest systolic value was used to collect an average of three readings taken at 120-s intervals.

Session 2 first reviewed the effectiveness of the implementation intentions plan and any barriers/difficulties in following it, and any required changes were developed collaboratively, following the methods outlined by Sniehotta [24]. This approach helped ensure that the patient had developed a suitable implementation intentions plan before adherence measurement commenced.

The main focus of session 2 was to elicit and, if appropriate, challenge any mistaken beliefs about a patient's *illness* (e.g. causes/effects of their stroke) and/or *medication* (e.g. beliefs regarding toxicity, dependence, etc.), using responses on the BMQ and BIPQ as a basis. This approach was based on the model of Petrie et al. [25] who elicited and modified patients' dysfunctional beliefs regarding their recent myocardial infarction, resulting in faster return to work and lower angina symptoms at 3 months. Our aim was to correct any misperceptions and provide evidence so that participants' medication *necessity* beliefs regarding their stroke medication came to outweigh their medication *concerns* beliefs. As an example, many patients did not understand why, as their cholesterol level was in the 'normal' range (i.e. 5.0 or less), they needed to take statins, which

they believed were very likely to result in adverse side effects (resulting from negative reports regarding statins in the UK media). In these instances, the research fellow aimed to increase the patients' belief in the necessity of their medication by informing them of the current recommendations for patients who have had a TIA or stroke (e.g. 'A statin should be prescribed to patients who have had an ischaemic stroke, irrespective of cholesterol level' [26]) and explaining that having a cholesterol level of 4.0 or lower was likely to further reduce their risk of having another TIA or stroke. The research fellow also provided information on the likelihood of experiencing any side effects mentioned (e.g. less than one in ten people report experiencing this side effect).

Control Condition The use of an objective outcome measure of adherence in both groups, to control for any measurement effect of using the MEMS pill bottle, meant we were not able to have a 'usual care' group. Hence, control group participants received the same number of visits by the research fellow, and all measures including BP readings were collected at the same time points as the intervention group. During the first two sessions, the research fellow engaged the patient in non-medication-related conversation (e.g. what had happened when they had their stroke) to control for non-specific effects of attention/social contact.

Both Groups At the end of session 2, the research fellow filled each participant's MEMS pill bottle with 1 month's supply of a single antihypertensive medication. For patients on more than one antihypertensive, the medication chosen was that taken most frequently (i.e. twice rather than once a day) or, if no difference, that which would most conveniently fit into the MEMS pill bottle. Patients were instructed to only take out one dose of their medication whenever they opened the pill bottle.

For each of the next 2 months, the research fellow made another brief visit to refill the MEMS pill bottle and also take an electronic reading from the MEMS cap, downloading the data onto a laptop PC for later analysis. The participant also completed the BIPQ, BMQ and perceptions of medication benefits measures at the first of these visits. At 3 months, the research fellow made a final visit to take a last MEMS cap reading, collect the MEMS pill bottle and final outcome measures and take the patient's BP.

Randomisation

Patients were randomised by the web-based Edinburgh Clinical Trials Unit software to either the intervention or control arm using a minimisation algorithm, together with a random element giving a one in ten chance of

allocation to the opposite treatment from that determined by the algorithm. Based on our previous study, the minimisation variables (chosen to ensure that the treatment arms did not differ on factors that might affect adherence) were age, MARS scores and complexity of the medication regime [13].

As this was a pilot study, the recruitment, intervention, data collection and analysis were all carried out by the same research fellow who was not blind to the treatment allocation. Patient contact time was controlled between treatment arms, and patients themselves were not informed which arm they were in.

Training of the Research Fellow

The research fellow was trained in the intervention by the principal investigator, who had been previously trained in the intervention used by Petrie et al. [25] in eliciting and addressing mistaken beliefs. Both the intervention and control group sessions (1 and 2) were piloted via role-play with the principle investigator acting as a pseudo-patient. These sessions were video-recorded, and feedback was given to the research fellow, after which minor modifications were made to the procedure.

Fidelity of Intervention Check

The principle investigator checked the transcriptions of sessions 1 and 2 for the first 11 participants in the intervention group (i.e. 38 % of all interviews) for adherence to the study protocol on an ongoing basis. Minor suggestions and modifications were made to subsequent sessions, but there were no violation issues. The fidelity check was terminated after the 11th interview, as no issues arose from the last four interviews checked (i.e. 8–11).

Statistical Analysis

Four people randomised to treatment did not use the MEMS pill bottle (three became ineligible between randomisation and the intervention and one declined to use the MEMS pill bottle at session 2) (Fig. 2). An a priori decision had been made to exclude all participants with no data on the primary outcome measure (MEMS) from the analysis, in accordance with our published protocol [16]. The remaining participants were analysed as allocated to the treatment arm ($n=29$ in each group).

Missing Data

Four (6.9 %) of the 58 people included in the analysis discontinued participation in the study, all for reasons unrelated to the study aim, meaning that the data can be considered 'missing at random' [27] (i.e. 3 hospitalised for non-stroke reasons and 1 relocated). A further person chose to terminate a month early (for travel/time reasons) but completed all outcome measures at session 4 (defined completer).

There were no differences with regard to patterns of missing data and treatment group ($\chi^2(2)=0.5$, $p=0.766$) nor with regard to any of the pretreatment outcome measures, gender, Scottish Index of Multiple Deprivation (SIMD) scores, MMSE scores or overall MEMS scores (data available from the authors). Dropouts had lower pretreatment MARS scores, but there were no differences by treatment group.

Analysis

Missing data were addressed by multiple imputation, which is currently the preferred method of imputing missing data. Multiple imputation has been shown to perform well with both longitudinal data and small samples [28]. We used Imputation of Chained Equations in the STATA software package to impute five datasets which were then analysed using SPSS version 19. T tests and χ^2 were used to test basic differences between treatment groups, and repeated-measures analysis of variance was used to compare changes in outcome measures over time. Where required, test statistics were pooled using Rubin's rules [29].

Results

Part 1 (Screening for Intervention)

Overall, 494 people completed consent forms for part 1, 35 of these opted not to take part and 52 proved ineligible (50 previous stroke/TIA and 2 no stroke diagnosis). Questionnaires were, therefore, sent to 407 patients at a mean of 132 days (SD, 76.5) after their stroke/TIA; 355 questionnaires (87.2 %) were returned.
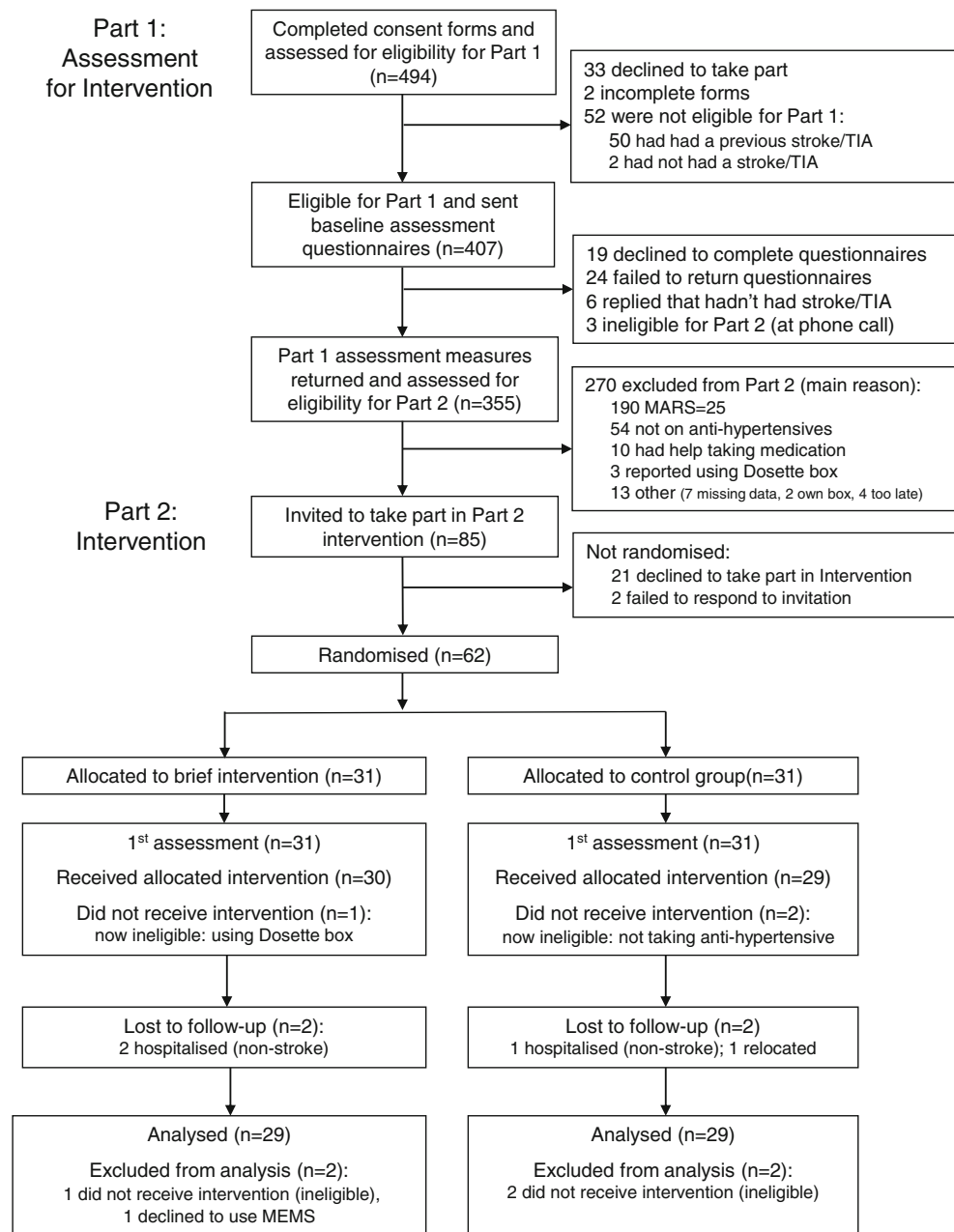
Two hundred seventy people were excluded from part 2 for reasons including maximum MARS adherence (53.5 %), not taking antihypertensives (20.6 %), receiving help taking their medication (11.0 %) and using a pharmacy-supplied Dosette box (23.7 %) (Fig. 2).

Part 2 (Intervention Versus Control)

Part 2: Participation

Eighty-five people were invited to take part in the intervention; 62 consented and were randomised to either the

Fig. 2 CONSORT diagram

Part 1:
Assessment
for Intervention

Completed consent forms and
assessed for eligibility for Part 1
(n=494)

33 declined to take part
2 incomplete forms
52 were not eligible for Part 1:
  50 had had a previous stroke/TIA
  2 had not had a stroke/TIA

Eligible for Part 1 and sent
baseline assessment
questionnaires (n=407)

19 declined to complete questionnaires
24 failed to return questionnaires
6 replied that hadn't had stroke/TIA
3 ineligible for Part 2 (at phone call)

Part 1 assessment measures
returned and assessed for
eligibility for Part 2 (n=355)

270 excluded from Part 2 (main reason):
  190 MARS=25
  54 not on anti-hypertensives
  10 had help taking medication
  3 reported using Dosette box
  13 other (7 missing data, 2 own box, 4 too late)

Part 2:
Intervention

Invited to take part in Part 2
intervention (n=85)

Not randomised:
  21 declined to take part in Intervention
  2 failed to respond to invitation

Randomised (n=62)

Allocated to brief intervention (n=31)

1st assessment (n=31)
Received allocated intervention (n=30)
Did not receive intervention (n=1):
now ineligible: using Dosette box

Allocated to control group (n=31)

1st assessment (n=31)
Received allocated intervention (n=29)
Did not receive intervention (n=2):
now ineligible: not taking anti-hypertensive

Lost to follow-up (n=2):
2 hospitalised (non-stroke)

Lost to follow-up (n=2)
1 hospitalised (non-stroke); 1 relocated

Analysed (n=29)
Excluded from analysis (n=2):
1 did not receive intervention (ineligible),
1 declined to use MEMS

Analysed (n=29)
Excluded from analysis (n=2):
2 did not receive intervention (ineligible)

intervention or the control group (Fig. 2). Three people were excluded after randomisation and before starting the intervention: one (intervention) had started using a Dosette box before the research fellow's first visit and two (both control) were no longer taking antihypertensive medication; therefore, 59 people started the intervention.

There were no major differences with respect to age, gender or any of the pretreatment beliefs measures between participants (n=59) and non-participants (n=296) (data available from the authors). However, part 2 participants (mean SIMD score=10.5 (SD, 9.6)) were from areas of lower deprivation than non-participants (mean=14.3 (SD, 13.3), 95 % CI for difference (0.9, 6.7); p=0.011).

Part 2 participants reported taking a mean of 5.5 (SD, 2.3; range, 2–15) different regular oral medications, representing a mean of 6.8 (SD, 4.1; range, 2–24) tablets each day, and a mean of 1.7 (SD, 1.0; range, 1–4) antihypertensive medications per day.

Baseline characteristics were similar in the intervention and control groups, suggesting that the randomisation procedure was effective (Table 1). Total contact time was not significantly different between the intervention (mean, 224 min (SD, 50)) and control (mean, 197 min (SD, 45)) groups (95 % CI for difference (−1, 55); p=0.056)). The slightly longer contact time in the intervention group largely occurred across sessions 1 and 2, when the intervention was

Table 1 Demographics and baseline outcome measures by intervention group (*n*=58)

	Intervention	Control
Age	68.4 (11.3)	70.7 (10.5)
	Range, 51–85	Range, 51–85
Gender (% male)	69 %	59 %
Ethnicity (% White British)	100 %	100 %
SIMD score (high=higher deprivation)	9.3 (10.8)	11.8 (8.4)
Work status[a]	58 % retired	60 % retired
	23 % working	30 % working
FAST total score	19.0 (1.1)	18.7 (1.1)
MMSE	28.6 (1.3)	28.3 (1.3)
Type of stroke (% ischaemic)	100 %	100 %
Stroke severity[b]		
TIA	31.0 %	48.3 %
Minor/small stroke	20.7 %	10.3 %
Stroke	48.3 %	41.4 %
Days from stroke to randomisation	191 (84)	162 (77)
Total no. of different medications	4.8 (1.8)	6.0 (2.6)
No tablets per day×frequency	15.1 (9.6)	19.2 (15.7)
Total number of BP medications	1.5 (0.7)	1.9 (1.1)
Total contact time (min)	224 (50)	197 (45)
BIPQ timeline	3.7 (3.8)	3.1 (3.4)
BIPQ treatment control	7.5 (2.3)	7.7 (2.3)
BMQ-specific—necessity subscale	17.4 (3.1)	18.1 (3.0)
BMQ-specific—concerns subscale	13.2 (3.2)	12.9 (3.4)
BMQ-necessity minus concerns	4.2 (4.5)	5.3 (4.6)
Perception of benefits of medication (%)	81.9 (19.0)	79.1 (21.2)
MARS unintentional non-adherence (item 1)	3.8 (0.4)	3.8 (0.5)
MARS intentional non-adherence (items 2–5)	19.4 (1.3)	19.3 (1.4)
MARS total score	23.3 (1.2)	23.1 (1.6)

SIMD Scottish Index of Multiple Deprivation, with lower scores equated to lower deprivation, *FAST* Frenchay Aphasia Screening Test, *MMSE* Mini-Mental State Examination, *BIPQ* Brief Illness Perception Questionnaire: timeline and treatment control subscales are reported as they have shown associations with adherence in previous research [13], *BMQ* Beliefs about Medication Questionnaire, *MARS* Medication Adherence Report Scale

[a] Those not working or retired were housewives, unemployed or on incapacity benefit

[b] As recorded by the consultant at the stroke unit in the letter to the patient's general practitioner

delivered; we, therefore, estimate that the active part of the brief intervention lasted, on average, <30 min.

Part 2: Primary Outcome Measure (MEMS)

MEMS data were recorded for a period of 3 months (mean number of days=82.2 (SD, 17.4); range, 16–90). The intervention group had higher adherence on all three MEMS outcome measures than the control group (Table 2), although this was only significant for doses taken on schedule (Fig. 3) (i.e. percentage of doses taken on schedule: mean difference, 9.8 %; 95 % CI (0.2, 16.2); *p*=0.048; percentage

of total doses taken: mean difference, 5.1 %; 95 % CI (−1.6, 9.0); percentage of days correct dose taken: mean difference, 5.4 %; 95 % CI (−1.8, 9.4)). There were no effects of time or the group×time interaction in any of the MEMS analyses.

Part 2: Secondary Outcome Measures

MARS Scores Table 3 shows the changes in scores in self-reported adherence (MARS) from pre-intervention to follow-up. There were significant time and interaction effects of total MARS scores, with both groups reporting

Table 2 Mean (SD) MEMS readings by time and treatment group (*n*=58)

		Month 1	Month 2	Month 3	Pooled *F*		
					Group×time	Group	Time
% Doses taken	Intervention	98.8 (2.1)	99.0 (2.2)	99.0 (2.1)	1.6, *p*=0.267	2.0, *p*=0.163	0.6, *p*=0.572
	Control	94.1 (15.5)	92.8 (16.5)	94.7 (14.2)			
% Days correct dose taken	Intervention	98.6 (2.2)	99.0 (2.2)	98.7 (2.0)	1.6, *p*=0.229	1.9, *p*=0.178	0.5, *p*=0.662
	Control	93.7 (15.4)	92.6 (16.5)	94.0 (14.4)			
% Doses taken on schedule	Intervention	95.9 (5.8)	97.4 (3.1)	96.8 (3.6)	0.9, *p*=0.456	4.3, *p*=0.048	0.6, *p*=0.555
	Control	86.9 (22.2)	86.6 (22.5)	87.4 (23.3)			

df for *F* are adjusted by inter-imputation variance to give pooled *p* values and, therefore, vary for each statistic

higher adherence at follow-up, but a significantly greater improvement in the intervention group (mean difference, 0.61; 95 % CI (0.1, 1.2); *p*=0.027).

Self-reported adherence (i.e. MARS total scores) at follow-up was highly correlated with all objective MEMS measures (all *p*<0.001), i.e. percentage of doses taken (*r*=0.71), percentage of days correct dose taken (*r*=0.70) and percentage of doses taken on schedule (*r*=0.66).

Blood Pressure Both groups showed a reduction in BP readings, with a significant effect of time on both systolic and diastolic measures (Table 3), but there were no differences between groups.

Beliefs About Illness and Medication Table 4 shows the pre, post and follow-up scores on the BMQ-specific subscales. There was a significant effect of time with BMQ-necessity minus concerns increasing and BMQ-concerns decreasing from pretreatment to follow-up in both groups. BMQ-concerns also showed a significantly greater decrease by

follow-up in the intervention versus the control group (mean difference, 1.3; 95 % CI (0.1, 2.5); *p*=0.047). There were no significant effects of changes in beliefs about illness (BIPQ) or perceived benefit of medication as a result of the intervention (Table 4).

Discussion

This simple, brief, two-session intervention resulted in a 10 % increase in doses of antihypertensive medication taken on schedule. This level of increase is likely to be clinically important, as a large (*n*=47,479) retrospective cohort study, using medical and pharmacy records to assess health outcomes and adherence over 1–5 years, concluded that 'increasing adherence by one (anti-hypertensive) pill per week for a once-a-day regimen reduces the hazard of stroke by 8–9 % and death by 7 %' [14]. Furthermore, the main effect was observed on doses taken on schedule, precisely what the implementation intentions intervention aimed to change. We also achieved our aim of a greater reduction in concerns

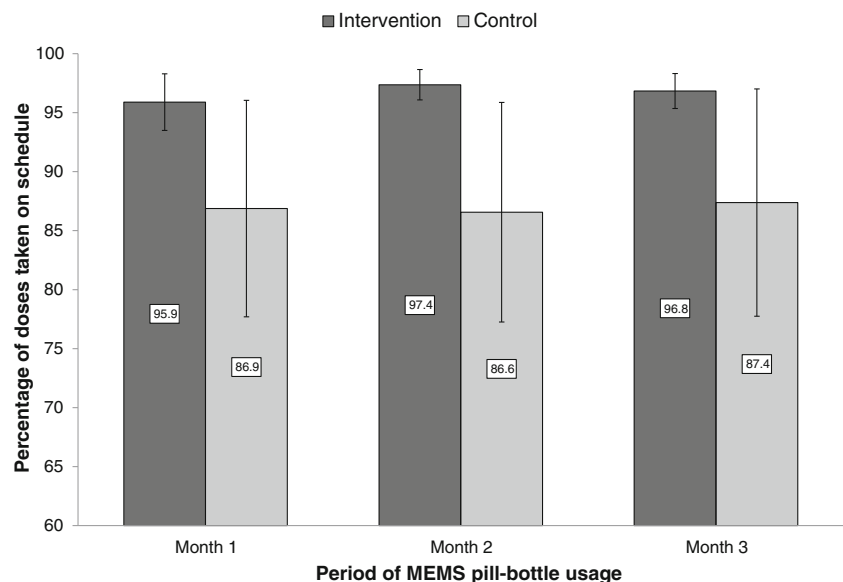**Fig. 3** Percentage of doses taken on schedule by treatment group for months 1–3

Table 3 Mean (SD) MARS adherence scores and BP readings by time and treatment group (n=58)

		Pre	Follow-up	Pooled F		
				Group×time	Group	Time
MARS total	Intervention	23.3 (1.2)	24.2 (0.5)	4.9, $p=0.027$	2.0, $p=0.154$	18.8, $p<0.001$
	Control	23.1 (1.6)	23.6 (1.3)			
BP systolic (mmHg)	Intervention	133 (18)	131 (17)	3.5, $p=0.110$	1.2, $p=0.319$	8.5, $p=0.018$
	Control	141 (22)	132 (20)			
BP diastolic (mmHg)	Intervention	81 (11)	80 (11)	2.7, $p=0.112$	0.1, $p=0.710$	7.0, $p=0.049$
	Control	83 (13)	79 (13)			

df for F for MARS scores are adjusted by inter-imputation variance to give pooled *p* values and, therefore, vary for each statistic; BP was measured as an average of three readings taken from the arm which initially showed the highest single reading at the first visit. The same arm was used for the average readings at both pre and follow-up

about medication in the intervention versus the control group.

Previous interventions to improve adherence have had mixed results [4, 30], although adherence in clinical trials is often higher than expected [31]. Implementation intentions interventions in other health conditions have been successful in improving adherence to medication in some (e.g. antiepileptic drugs [10]), but not all (e.g. antibiotics [31]) studies. A recent RCT aimed at reducing concerns about medication in 136 non-compliant hypertensive patients in Jordan was strongly associated with higher adherence and reductions in BP [32]; however, this study did not control for patient contact time. In contrast, a controlled UK-based nurse-led support intervention which encouraged hypertensive patients to discuss their medication concerns showed no effects on either adherence or BP [33].

The current study, using electronic pill monitoring, found high levels of adherence overall, in contrast to some other studies of adherence in stroke patients [6]. Patients' adherence did not appear to become worse over the 3 months of MEMS pill bottle usage nor were there any differences in adherence over time between groups, contrary to our expectation of a Hawthorne (or mere measurement) effect [17]. It is important to emphasise that we did not compare our brief intervention with treatment as usual; rather, our control condition involved significant additional contact and electronic recording of pill-taking for 3 months. It is highly likely that this resulted in improved adherence in the control group, e.g. when asked to rate the MEMS pill bottle during the follow-up interview, 46 % of control participants reported that they found it helpful regarding adherence. This may also account for the fact that, although the intervention group were significantly more regular in their pill-taking than the control group, the differences in pills taken (i.e. 5 % more in the intervention group) was non-significant. Although, due to cost, we were only able to use the MEMS pill bottle for one medication (a single

Table 4 Mean (SD) scores for medication and illness beliefs by time and treatment group (n=58)

		Pre	Post	Follow-up	Pooled F		
					Group×time	Group	Time
BMQ-specific necessity	Intervention	17.4 (3.1)	18.1 (2.6)	18.5 (2.5)	0.8, $p=0.460$	0.1, $p=0.743$	2.7, $p=0.066$
	Control	18.1 (3.0)	17.9 (3.0)	18.5 (2.7)			
BMQ-specific concerns	Intervention	13.2 (3.2)	11.9 (3.7)	11.0 (2.5)	3.1, $p=0.047$	0.01, $p=0.924$	9.2, $p<0.001$
	Control	12.9 (3.4)	11.7 (3.7)	11.9 (3.0)			
BMQ-necessity minus concerns	Intervention	4.2 (4.5)	6.1 (4.9)	7.4 (3.4)	2.5, $p=0.081$	0.02, $p=0.879$	10.8, $p<0.001$
	Control	5.3 (4.6)	6.2 (4.9)	6.6 (4.3)			
BIPQ-timeline	Intervention	3.7 (3.8)	4.4 (4.0)	4.1 (3.7)	0.9, $p=0.418$	2.3, $p=0.132$	0.1, $p=0.952$
	Control	3.1 (3.4)	2.6 (3.2)	3.0 (2.9)			
BIPQ-treatment control	Intervention	7.5 (2.3)	8.2 (2.0)	8.7 (2.2)	1.8, $p=0.160$	0.7, $p=0.417$	1.4, $p=0.256$
	Control	7.7 (2.3)	8.0 (2.3)	7.7 (1.9)			
% Perceived benefit	Intervention	81.9 (19.0)	81.1 (15.9)	84.8 (15.7)	1.2, $p=0.328$	0.3, $p=0.622$	0.3, $p=0.758$
	Control	79.1 (21.2)	82.5 (19.1)	81.4 (17.4)			

df for F are adjusted by inter-imputation variance to give pooled *p* values and, therefore, vary by each statistic. Timeline and treatment control subscales are reported as they have shown associations with adherence in previous research [13]

BMQ Beliefs about Medication Questionnaire, *BIPQ* Brief Illness Perception Questionnaire

antihypertensive), all patients took a number of medications (range, 2–15), often at the same time. From the detailed conversations the research fellow had with patients throughout the study, we have no reason to believe that using the MEMS pill bottle for only one antihypertensive negatively impacted on other medication-taking nor that it resulted in patients being any more or less adherent to their remaining medicines.

The intervention did not significantly increase patients' beliefs in the necessity of their medication; rather, the effect was a reduction in concerns. However, as many of the patients had been on multiple preventive medications such as antihypertensives and statins for some years, many already viewed their treatment as 'necessary'.

Baseline data were not recorded for the MEMS and so the apparent differences between groups from month 1 may well reflect an immediate effect of the intervention on adherence. The significantly greater improvement in self-report adherence (MARS) in the intervention group from pretreatment to follow-up supports this observation.

Although the greater increase in MARS total scores from pretreatment to follow-up in the intervention group did not translate into greater reductions in BP, both groups did show a significant reduction over time, which may be due to the relatively high adherence observed in both groups.

Limitations

A limitation of the current study was that the same research fellow delivered the intervention and conducted the analysis and so was not blind to the treatment arm of the patients. However, the main outcome measure was electronically recorded MEMS readings, and the remaining (self-report) outcome measures were posted out to and completed by patients in advance of the meetings with the research fellow, so we do not believe that this would have greatly affected the results. As we did not collect baseline MEMS readings, it is possible that the differences found may have been observed at pretreatment and not as a result of the intervention. However, there were no differences between groups in baseline self-reported adherence (MARS) and we did observe significantly higher increases in MARS scores in the intervention group, suggesting that this was not the case.

We planned to recruit patients 3 months after their stroke, to allow time for the establishment of medication routines; however, many patients were prescribed antihypertensives before their stroke and so the intervention may be more effective if delivered earlier. All participants were White British, had had an ischaemic stroke and tended towards higher socio-economic status; thus, the intervention warrants evaluation with more diverse populations. However, although those from more deprived areas reported lower adherence overall, socio-demographic status was not related

to increases in self-reported adherence from pretreatment to follow-up, suggesting that our intervention may be effective across social domains. We also acknowledge that other factors that were not measured in the current study, such as depression and social support, may also contribute to non-adherence of medication.

Conclusions

The current study has shown that a combined brief intervention which addresses patients' erroneous beliefs about medication and stroke to reduce intentional non-adherence, in conjunction with introducing an implementation intentions plan to reduce forgetting, can improve adherence to preventive medication by 10 % in an older population of stroke patients, over and above any effects of measurement or high therapeutic contact. The effect found was equivalent to taking one additional dose in ten within ±3 h of a regular time.

Using plans to establish routines may help older adults adhere to time-regulated tasks by making them automatic habits, whilst addressing patients' concerns may result in less reluctance to take medication. It has also been suggested that negative views about treatment may underlie unintentional, as well as intentional, reasons for not taking medication [34]; thus, it is plausible that the observed reduction in medication concerns led to decreases in both forgetting and choosing not to take medication in the current study.

This pilot was conducted in stroke survivors; however, it may well be generalizable to other patients on multiple medications. We estimate that the active part of the intervention took no more than 30 min, spread over sessions 1 and 2. Although our approach may be more resource-intensive than simpler interventions, such as telephone reminders or mobile phone alarms, our findings suggest that it is important to address not just non-intentional adherence but also intentional adherence by eliciting and addressing patients' underlying beliefs which are likely to affect their medication-taking. Hence, there remains a need for personalised interventions to increase adherence. We believe that this simple, relatively brief intervention could address this need, particularly if delivered in a healthcare setting at the time when medication for a chronic condition was first prescribed.

We observed small to medium (0.17 to 0.59) effects on all the main outcome measures. Using G*Power [35] to estimate the sample sizes required to detect these effects in a larger-scale study, sample sizes varied from $n=102$ to $n=240$. Allowing for 20 % attrition, this would mean a total sample size of 288 patients would be large enough to detect the effects found in the current study. The next step, therefore, is to confirm this effect in an adequately powered RCT to demonstrate that the intervention can be successfully delivered by trained health professionals (e.g. nurses) in different healthcare settings.

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