

SYSTEMATIC REVIEW

A systematic review of the effectiveness of interventions to help older people adhere to medication regimes

NICOLA HIGGINS¹, CIARAN REGAN²

¹Health Service Research Department, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK

²Department of Psychiatry and Behavioural Sciences, University College London, Archway Campus, Holborn Building, Highgate Hill, London N19 5LW, UK

Address correspondence to: N. Higgins. Fax: (+44) 20 7277 1462. Email: n.higgins@iop.kcl.ac.uk

Abstract

Background: non-adherence is a common cause of treatment failure. The causes and context of non-adherence may differ amongst older people and reviews of interventions to improve adherence have tended to focus on the younger adult population.

Objective: to conduct a systematic review of interventions to aid adherence to medication for older people over the age of 65.

Method: relevant papers identified by searching the Cochrane Database of Systematic Reviews and the Database of Abstracts of Review of Effectiveness (Cochrane Library), Medline 1966–October 2002, Embase 1980–October 2002, Best Evidence, PsychINFO 1887–October 2002 and CINAHL 1982–October 2002. These were then hand-searched. The papers that fitted our inclusion criteria were selected. Two independent reviewers using an established tool assessed the studies for methodological quality. A non-statistical narrative approach was then taken to analyse the studies due to the heterogeneity of the outcome measures.

Results: 7 studies were identified. They used a variety of approaches involving external cognitive supports and/or educational interventions. Most studies were of poor methodological quality. Statistically significant effects, where present, tended to have small effects clinically.

Conclusions: currently there is no strong evidence to support the use of any one intervention type. Future research should use combinations of approaches, as there is some evidence that these are more likely to be successful.

Keywords: *older people, adherence, compliance, systematic review, drug treatment*

Introduction

Non-adherence or 'non-compliance' with medication is common. Around 40–60% of patients do not take medication as prescribed [1] and this can lead to treatment failure, further physical or mental health problems, service costs and carer burden [2]. As the over-65 population is the fastest growing cohort and the most likely population to be prescribed tablets, problems associated with non-adherence in this age group are likely to increase [3]. Effective adherence interventions to address this issue would therefore be valuable.

Adherence behaviour is a complex area with biomedical, psychological and anthropological explanations competing for attention. In general terms, patient attitudes, social circumstances, medication side effects and the nature of the patient–doctor relationship have been postulated as important influences [4].

Taking an overview of progress in this area is problematic. Non-adherence as a phenomenon spans medical disciplines

but research by its nature tends to be discipline specific in outlook, often limited to a specific diagnosis or medication; it can therefore be difficult to bring papers meaningfully together for meta-analysis [5]. A systematic review of adherence interventions looking at unconfounded randomised trials amongst the younger adult population found only 15 studies; seven demonstrated improved adherence, six of which led to improvements in treatment outcomes [2]. This review concluded that effective interventions were complex, combining approaches such as counselling, information, reminders and family therapy; statistically significant positive findings did not however lead to worthwhile improvements in clinical outcome. Most meta-analyses include only papers that are methodologically robust; however, as most research in this area is small scale, adherence is often a secondary outcome measure nested within a larger study, and the quality of papers tends to be poor [1]. As a consequence most relevant papers are excluded and therefore not disseminated in the literature beyond the confines of the medical discipline from

which they originated. A recent meta-analysis that did include less statistically robust papers amongst the younger adult population broadly agreed in its findings with the review described above, and concluded there was no clear advantage to any one strategy over another [5].

Extrapolating research findings from younger adults to older people is problematic. Older people may differ in their experience of illness and medication and, in addition, may share different tendencies in their attitudes towards adherence. Published research often excludes the older population, usually without justification [6]. Amongst the over-65 population, chronic illness, subtle or frank cognitive deficits, co-morbidity and associated complicated treatment regimes may all further complicate the picture [7]. This systematic review therefore specifically focuses on how to improve medication adherence amongst older people over the age of 65. We expected that effective adherence interventions would be complex, in keeping with findings amongst younger adults as described above. As the literature in this area is sparse this review is broad in scope, including all trials of adherence interventions for older people regardless of illness, treatment setting or intervention type used.

Method

Inclusion criteria

The inclusion criteria were as follows: *firstly* a focus on the 65 and over age group, *secondly* demonstration of an intervention to improve medication adherence, *thirdly* the inclusion of a control group and *fourthly* publication in an English language journal between 1966 and 2002. Studies addressing adherence to interventions other than medication were excluded.

Search strategy

The following databases were searched using the terms *adherence, concordance, or compliance* and *older people, old age, geriatric or elderly*: The Cochrane Database of Systematic Reviews and the Database of Abstracts of Review of Effectiveness (Cochrane Library), Medline 1966–October 2002, Embase 1980–October 2002, Best Evidence and PsychINFO 1887–October 2002, CINAHL 1982–October 2002. Relevant studies, bibliographies, and reviews found were then hand-searched. Experts with research experience and publications in this field (Lynn Myers, Cornelius Katona and Gill Livingston) were contacted to check for unpublished material.

Data extraction and analysis

A data extraction form was developed to judge the methodological quality of the papers to allow the assessment of the studies to be reproducible. The methodological quality was judged on the basis of a tool developed by Nichol *et al.* 1999 [1] specifically for the evaluation of medication adherence interventions. The criteria used were as follows: *use of randomisation, description of randomisation procedure, blinding, power analysis, specification of patient sample, specification of illness, specification of therapeutic regime, duration of follow-up, clear definitions of adherence/adherence measurement and an account of all patients at the end of the*

study. Although this tool was originally used to calculate a composite score for methodological quality, this approach has not been used here: composite scores are often neither valid nor reliable in practice. There is also no gold standard for trial methodological quality as such [8]. The two authors of this study (N.H. and C.R.) assessed the studies' methodological quality independently using this tool. Discrepancies were subsequently resolved by referring to the original studies. A non-statistical narrative approach was used to analyse the data: given the heterogeneity of the outcome measures, the few papers involved and the overall poor statistical quality, a statistical meta-analysis was not appropriate.

Results

From the search, 1,925 study titles were identified using the above criteria. After screening these titles and reading all potentially relevant abstracts, 43 studies were judged potentially relevant. These were traced and read in full, leaving seven studies remaining that satisfied our inclusion and exclusion criteria.

The interventions fell broadly within two categories: *external cognitive supports* involving the mechanics of medication delivery and *education strategies*, though several interventions combined elements of both. Individual study characteristics are shown in Table 1 and their outcomes in Table 2. One study used physical aids to help organise and remind people about time and dose of medication: Ware *et al.* (1991) used calendar blister packs. Improvement in adherence occurred when the blister pack was combined with cognitive support. Education strategies varied considerably in nature and had mixed success. Information was provided in a variety of formats, including face-to-face instruction, telephone consultations and written information. In some instances education was provided as part of a package including self-medication programmes and pharmacist medication review.

The quality of the studies varied considerably, as shown in Table 3. All but one used randomisation, but the procedure used was described in only four (Lourens and Woodward, 1993; Levens-Lipton and Bird, 1994; Esposito, 1995; Nazareth *et al.*, 2001). Notably these were the only ones, apart from Esposito (1995), to use a power calculation for their sample sizes. Potential investigator bias was poorly addressed; only two studies (Levens-Lipton and Bird, 1994; Nazareth *et al.*, 2001) used a blind rater to assess outcome. Two of the studies assessed adherence based on tablet counts alone, three used patient interview alone and two combined both of these methods. Six of the studies calculated an adherence score using these measures but these varied in nature, as discussed below. One of the studies simply generated dichotomous categories of 'compliant' and 'non-compliant' patients. Two of the seven had short follow-up periods of a month or less, one study had a follow-up period of between 3 and 6 weeks. None of the studies used an intention to treat analysis, whereby patients who withdraw are analysed in the group to which they were originally allocated.

It is of note that during our search we identified several studies that were focused on older adults but had younger age criteria (e.g. 55 years and over) than studied here (65 years

Table I. Study description

Study	Medication	Discipline	Setting	Study groups
Ware <i>et al.</i> , 1991	Any	Pharmacist	Hospital inpatients	1. Self-medication programme, medication cards 2. Self-medication programme, medication cards & unit-of-use packaging
Wolfe and Schirm, 1992	Cardiac mainly	Nursing	Hospital inpatients	1. Medication counselling with written aid 2. Ill defined: 'control group did not have counselling' but it is not stated clearly whether the written aid was provided for the control group
Lourens and Woodward, 1993	Any	Pharmacist	Hospital outpatients	1. Counselling 2. Counselling & medication card
Levens-Lipton and Bird, 1994	Any except psychiatric; <i>No justification for exclusion given</i>	Pharmacist	Hospital inpatients	1. Medication booklet 2. Medication booklet, medication review, 1 face-to-face inpatient & 3 post-discharge telephone consultations
Esposito, 1995	Any	Nurse	Hospital inpatients	1. Medication fact sheet and discharge sheet 2. Medication fact sheet & verbal instruction 3. Medication schedule in large lettering with a list of side-effects and dosage schedule 4. Medication schedule and verbal instruction
Lowe <i>et al.</i> , 2000	Any	Pharmacist	General practice	1. 3 home visits delivering medication 2. 3 home visits delivering plus reviewing medication & patient education
Nazareth <i>et al.</i> , 2001	Any	Pharmacist	Hospital inpatients with at least 4 drugs	1. Treatment as usual 2. Medication review, information provision, carer liaison, medication plan copied to patient, community pharmacist and GP & post-discharge home visit

and over). These studies appeared to be similar in the type of approaches used and their methodological difficulties as those described above.

Discussion

Overall the findings of this review echo the meta-analyses of adherence interventions in younger adults outlined above. Firstly our initial belief was upheld, i.e. effective interventions were complex. Single discrete interventions were disappointing and positive effects were only found with combinations of approaches. Secondly, results were mixed and statistically significant positive effects tended, clinically, to be small. Thirdly, a consistent finding was that generally studies were not of a high standard methodologically (with randomisation, blind raters, power analyses, specified patient samples, all patients being accounted for, intention to treat analyses, recognised outcome measurements and clearly defined objectives), with the notable exception of Nazareth *et al.* (2001), which found no significant effect for their intervention. Interestingly, this paper is the most recent to be published.

The applicability of controlled trials to investigate complex interventions in psychiatry has been called into question [9]. Firstly, it is notoriously difficult to standardise interactions with patients. The studies employing some form of education were not clear as to how this was provided, e.g. the degree to which sessions were didactic in

nature. It is of note that all the educational interventions bar two (Esposito, 1995; Wolfe and Schirm, 1992) were provided by pharmacists who may not have clinical experience. Thus it is difficult to bring these studies together as evidence for the utility (or otherwise) of educational approaches. In addition the reproducibility of the interventions in one's own clinical practice is difficult to gauge. A second problem with complex interventions is that they contain multiple elements, such as oral instruction and medication reviews; it is therefore difficult to conclude what aspects are effective or otherwise. Many of these studies blended elements that individually might appear to be common sense, for instance the conversion of complex regimes to twice daily dosing. This is an intuitively appealing idea, argued by some to be the single most important approach to improving adherence [10].

There was an implicit aetiological assumption underpinning all the interventions, mainly that non-adherence stems from a lack on the patient's behalf—either of knowledge or cognitive organisation—to be remedied by appropriate supplementation. This approach originates from within the classical biomedical paradigm. In the studies under consideration here, information appears to have been administered as if analogous to a discrete pharmaceutical intervention. That is to say the patient has been understood to be a passive recipient, with the context for this process as irrelevant 'noise' in the study design to be adjusted for in the analysis. None of the interventions directly tackled the issue

Table 2. Adherence assessments and outcomes

Study	Quantitative adherence measure	Statistically significant improvements in adherence compared with controls
Ware <i>et al.</i> , 1991	No: dichotomous outcome of 'compliant' (taking all tablets prescribed) or 'non-compliant' based on a tablet count and patient interview	Improvement in group 2 with adherence 86.7% <i>vs</i> 66.67% in group 1 at discharge; 48.9% <i>vs</i> 23.1% at 3 months ($P \leq 0.05$)
Wolfe and Schirm, 1992	Yes: the 'Medication Rating Scale' (MCRS) – this provided continuous data on level of compliance. Subjects were asked regarding their medication: name, dose, unit, frequency, indication for use and duration	No significant improvement in either group post counselling or at follow-up
Lourens <i>et al.</i> , 1993	Yes: adherence = (sum of all expected doses – absolute deviation from expected doses) / (sum of all expected doses taken) $\times 100\%$. Based on a tablet count	No improvement despite improvement in knowledge compared to group 1
Levens-Lipton and Bird, 1994	Yes: 5 dimensions of adherence assessed including knowledge. Composite score = 'number of compliance dimensions multiplied by the number of drugs to be analysed to yield the total number of cells and then the number of cells scored as compliant / total number of cells and multiplied by 100'. Based on patient interview	Improvement in group 2 with adherence 96.3% <i>vs</i> 91.2% in group 1 ($P \leq 0.001$)
Esposito, 1995	Yes: Medication adherence score was generated using pill counts and self-reports: (d1)(a1) + (d2)(a2) + = d number of doses to be taken; a adherence rate d1 + d2 +	None
Lowe <i>et al.</i> , 2000	Yes: adherence = (number of tablets taken/the correct number) $\times 100\%$; mean adherence score then calculated. Based on a tablet count	Improvement in group 2 with adherence 91.3% (95% CI 88.7%–93.9%) <i>vs</i> 79.5% (95% CI 74.7%–84.3%) in group 1 ($P < 0.0001$)
Nazareth <i>et al.</i> , 2001	Yes: knowledge and adherence assessed to generate a composite score. Based on patient interview	None

Table 3. Methodological quality and statistical outcome

Study	i. Randomised ii. Randomisation process described iii. Blinding	Power analysis	Adherence defined	Specified patient sample	Length of follow-up	All patients accounted for at the end of the study	Intention to treat analysis	Number of patients in each arm
Ware <i>et al.</i> , 1991	No – cross over study of wards N/A No	Yes	Yes	Yes	3 months	Yes	No	Group 1: $n = 45$ Group 2: $n = 39$
Wolfe and Schirm, 1992	No No No	No	Yes	Yes	3–6 weeks	Yes	No	Group 1: $n = 25$ Group 2: $n = 25$
Lourens and Woodward, 1993	Yes: clinics Yes No	No	No	No	1 month	Yes	No	Group 1: $n = 49$ Group 2: $n = 48$
Levens-Lipton and Bird, 1994	Yes: patients Yes Yes:- investigator	No	No	Yes	3 months	No	No	Group 1: $n = 109$ Group 2: $n = 124$
Esposito, 1995	Yes: patients Yes: block No	No	No	Yes	2 months	Yes	No	Group 1: $n = 11$ Group 2: $n = 8$ Group 3: $n = 10$ Group 4: $n = 14$
Lowe <i>et al.</i> , 2000	Yes: patients No No	Yes	No	No	1 month	Yes	No	Group 1: $n = 84$ Group 2: $n = 77$
Nazareth <i>et al.</i> , 2001	Yes: patients Yes Yes	Yes	No	Yes	6 months	Yes	No	Group 1: $n = 181$ Group 2: $n = 181$

that a patient might actively choose not to take medication and none sought to elicit patients' attitudes to medication as a potential mediator of adherence.

There was a lack of consensus as to how adherence should be calculated. The gold standard has been argued to be serum or urine analysis, but this is invasive and complicated by individual differences in drug metabolism [11]. Such techniques also implicitly reject patient self-report, taking a stance that now seems paternalistic and outdated—no study here employed such methods. Each study devised their own idiosyncratic scoring system, ranging from dichotomous 'adherent' or 'non-adherent' outcomes to complex calculations, used in conjunction with pharmacist tablet count or patient self-report. This variation makes comparison between study adherence outcomes difficult and whilst dichotomous measures may over-simplify, complex calculations made analysis unwieldy and, at points, confusing.

The control groups were all markedly adherent, in keeping with younger adult study populations. This may in part be due to the Hawthorne effect, i.e. the effect of being observed in a study. Those agreeing to take part may also represent the more engaged and adherent end of the patient spectrum. Only two studies (Esposito, 1995; Nazareth *et al.*, 2001) actually assessed patients' cognitive function as a potential confounder, despite the methodology of several of the studies implying that lack of cognitive organisation was aetiologically important in this group (reflecting perhaps a stereotype of older people as cognitively impaired).

One might assume that a strategy leading to improved adherence would ultimately lead to health care savings but only the Levens-Lipton and Bird (1994) study performed a thorough cost-analysis to test this. They found that although adherence improved with their intervention this did not translate into fewer hospital admissions or subsequent lower costs. The difference between a statistically significant and economically significant result is pertinent here.

The results of this review do not lend support for the common assumption that adherence will follow knowledge or justify improving knowledge for its own sake. This is perhaps not surprising when one considers that knowledge is of little use to a patient if they do not believe it pertains to them. Testing knowledge may, theoretically at least, be stressful for a patient and therefore raises ethical issues. It is interesting to note a Cochrane review's ethical guidelines on adherence intervention trials develop this argument further by stipulating that adherence by itself is not a justifiable end-point but should be measured in combination with meaningful clinical outcomes [2]. Only one study here took such a broader perspective; Levens-Lipton and Bird (1994) analysed hospital service use alongside adherence and medication knowledge.

Limitations of this review

The main limitation of this overview was that the search was limited to English language publications. In addition the review focused on interventions to improve medication adherence; any potentially relevant interventions to improve adherence with other health care interventions, such as diet or exercise, were therefore not included.

Conclusion

There is not yet any strong evidence to support the use of any one type of intervention to help improve adherence amongst older people. Most research thus far has not been of a high standard methodologically and is difficult to bring together due to the heterogeneity of the studies involved. This said, the findings of this review do suggest that there may well be a role for cognitive supports and educational interventions. It would therefore be worth investigating these approaches further in future with well-designed studies that address possible confounding factors (e.g. cognition) and employ valid outcome measures. Most importantly for future research it is likely that successful interventions will be those employing sophisticated combinations of approaches tailored to a patient's individual needs.

Key points

- There are few published controlled trials of adherence interventions for people over the age of 65.
 - Studies thus far have tended to be of poor methodological quality and their results difficult to interpret clinically.
 - There is no robust evidence supporting any one type of approach.
 - Successful interventions are likely to be combinations of educational interventions and cognitive supports.
-

Acknowledgement

We would like to thank Dr Gill Livingston and Dr Martin Orrell for their support and advice throughout this project.

Studies reviewed

- Esposito L. The effects of medication education on adherence to medication regimens in an elderly population. *J Adv Nursing* 1995; 21: 935–43.
- Levens-Lipton H, Adair Bird J. The impact of clinical pharmacists' consultations on geriatric patients' compliance and medical care use: a randomised controlled trial. *Gerontologist* 1994; 34: 307–15.
- Lourens H, Woodward M. Impact of a medication care on adherence in older people. *Aust J Ageing* 1993; 13: 72–76.
- Lowe C, Raynor D, Purvis J *et al.* Effects of a medicine review and education programme for older people in general practice. *Br J Clin Pharmacol* 2000; 50: 172–75.
- Nazareth I, Burton A, Shulman S *et al.* A pharmacy discharge plan for hospitalised elderly patients – a randomised controlled trial. *Age Ageing* 2001; 30: 33–40.
- Ware G, Holford N, Davison J, Harris R. Unit dose calendar packaging and elderly patient compliance. *New Zealand Med J* 1991; 104: 495–7.
- Wolfe S, Schirm V. Medication counseling for the elderly: effects on knowledge and compliance after hospital discharge. *Geriatr Nursing* 1992; 13: 134–9.

References

1. Nichol M, Venturini F, Sung J. A critical evaluation of the methodology of the literature on medication compliance. *Ann Pharmacother* 1999; 33: 531–9.
2. Haynes B, McKibbin K, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet* 1996; 348: 383–6.
3. Ames D. Depression and the elderly. In Dawson A, Tylee A eds. *Depression: Social and Economic Timebomb*. London: BMJ Publishing Group, 2001.
4. Delado PL. Approaches to the enhancement of patient adherence to antidepressant medication treatment. *J Clin Psychiatry* 2000; 61: 6–9.
5. Roter D, Hall J, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance – a meta-analysis. *Medical Care* 1998; 36: 1138–61.
6. Bayer A, Tadd W. Unjustified exclusion of elderly people from studies submitted to research ethics committee for approval: descriptive study. *Br Med J* 2000; 321: 992–3.
7. Durso SC. Technological advances for improving medication adherence in the elderly. *Ann Long Term Care* 2001; 9: 43–48.
8. Greenhalgh T. How to read a paper: papers that summarise other papers (systematic reviews and meta-analyses). *Br Med J* 1997; 315: 672–3.
9. Holloway F. Outcome measurement in mental health; welcome to the revolution. *Br J Psychiatry* 2002; 181: 1–2.
10. Eisen SA, Miller DK, Woodward RS. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med* 1990; 150: 1881–4.
11. Kemp R, Hayward P, Applewhaite G, Everitt B, David A. Compliance therapy in psychotic patients: randomised controlled trial. *Br Med J* 1996; 312: 345–9.

Received 7 January 2003; accepted in revised form 25 November 2003