Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review

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Abstract Adequate adherence to medication regimens is central to the successful treatment of communicable and noncommunicable disease. Fixed-dose combination pills and unit-of-use packaging are therapy-related interventions that are designed to simplify medication regimens and so potentially improve adherence. We conducted a systematic review of relevant randomized trials in order to quantify the effects of fixed-dose combination pills and unit-of-use packaging, compared with medications as usually presented, in terms of adherence to treatment and improved outcomes. Only 15 trials met the inclusion criteria; fixed-dose combination pills were investigated in three of these, while unit-of-use packaging was studied in 12 trials. The trials involved treatments for communicable diseases (n = 5), blood pressure lowering medications (n = 3), diabetic patients (n = 1), vitamin supplementation (n = 1) and management of multiple medications by the elderly (n = 5). The results of the trials suggested that there were trends towards improved adherence and/or clinical outcomes in all but three of the trials; this reached statistical significance in four out of seven trials reporting a clinically relevant or intermediate end-point, and in seven out of thirteen trials reporting medication adherence. Measures of outcome were, however, heterogeneous, and interpretation was further limited by methodological issues, particularly small sample size, short duration and loss to follow-up. Overall, the evidence suggests that fixed-dose combination pills and unit-of-use packaging are likely to improve adherence in a range of settings, but the limitations of the available evidence means that uncertainty remains about the size of these benefits.

Keywords Drug packaging; Tablets/administration and dosage; Drug combinations; Self administration; Patient compliance; Treatment outcome; Randomized controlled trials; Review literature (*source: MeSH, NLM*).

Mots clés Emballage medicaments; Comprimé/administration et posologie; Association médicamenteuse; Auto-administration; Observance prescription; Evaluation résultats traitement; Essai clinique randomisé; Revue de la littérature (*source: MeSH, INSERM*).

Palabras clave Embalaje de medicamentos; Comprimidos/administración y dosificación; Combinación de medicamentos; Autoadministración; Cooperación del paciente; Resultado del tratamiento; Ensayos controlados aleatorios; Literatura de revisión (*fuente: DeCS, BIREME*).

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Introduction

Low adherence to prescribed self-administered medication is well documented and is particularly problematic in the treatment of chronic conditions (*1*, *2*). In developed countries, adherence to long-term therapy is estimated to average 50% (*3*). The implications of poor adherence are substantial at both the individual and population levels. For the patient, the benefits of treatment are reduced, leading to under-treatment of their condition and difficulties for the prescriber in assessing efficacy and appropriate dosage. At the population level, non-adherence results in medication wastage, increases in health-care costs, and drug resistance in the case of incompletely treated infectious conditions.

The causes of poor adherence are often complex. Patient-related factors have long been the focus of attention, but a multidisciplinary approach that considers such factors as only one of several important dimensions is now being advocated. A recent WHO report on adherence to long-term therapies (*3*) analysed contributing factors that were related to the specific condition being treated, health systems, social and economic conditions, and the therapy itself, as well as the contribution of the patient. The report indicated that the simplicity of the dosage regimen and side-effects were the therapy-related factors that had the greatest influence on adherence. The complexity of self-administration increases rapidly with the use of multiple therapies for the same condition or for several conditions in the same patient, and there is a consequent reduction in adherence (*3–7*). Therapy-related factors may therefore represent an important opportunity for improving adherence, and are also amenable to passive intervention.

One therapy-related intervention that aims to both simplify dosages and decrease side-effects is the development of

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fixed-dose combination pills, i.e. pills that include two or more drugs in fixed proportions in the same formulation. Such pills have been developed for the treatment of several diseases, being an important component of control of communicable diseases such as tuberculosis, and have recently been advocated for wider use in the treatment of noncommunicable disease (*8*, *9*). Given the issues raised by these combination pills for patients, physicians, manufacturers and regulators, the potential advantages of physically combining medications need to be quantified.

Along with manufactured fixed-dose combination pills, unit-of-use packaging is another intervention designed to reduce the complexity of self-administration of multiple medications, and therefore improve adherence. In this report, "unit-of-use packaging" includes blister packaging of several medications in fixed combination to be taken together (with or without calendar labelling) and the use of devices into which customized combinations of medications are loaded at regular intervals, to be self-administered according to calendar labelling.

We therefore conducted a systematic review of randomized controlled trials that compared medications combined in a single pill or medications combined within unit-of-use packaging (such as that recently approved for pravastatin and aspirin (*10*)) with the same medications in their usual presentation.

Methods

We sought to identify all randomized or quasi-randomized controlled trials that met the following criteria: participants were adult patients taking more than one oral self-administered medication, the intervention consisted of the use of a combination pill or unit-of-use packaging system compared with usual pill containers, and the study included at least one outcome measure relating to adherence, the pharmacological goal of medication (e.g. blood pressure control) or cost of therapy.

We conducted a search of the electronic databases MEDLINE (1966–May 2003), EMBASE (1980–May 2003), CINAHL (1981–May 2003), International Pharmaceutical Abstracts (1970–May 2003), the Cochrane Library (2003, Issue 2), and the metaRegister of Controlled Trials (mRCT) using the following keywords: compliance, adherence, fixed-dose combination, drug combination, unit-of-use, packaging, leprosy, malaria, tuberculosis, diabetes, hypertension, HIV.

Any article (including reviews) considered potentially relevant was retrieved, and the bibliographies of publications were examined for additional relevant studies. Web sites of institutions involved in research, policy and regulation relating to pharmaceuticals, and relevant conference web sites were also searched to identify trials. No language, date or publication restrictions were applied to the search.

Bioequivalence studies conducted for licensing purposes were not included because they lacked relevant outcome measurements. Trials of mixed interventions to improve compliance were excluded unless there were groups that differed only by one of the interventions under review.

All articles that described trials were assessed independently by two reviewers (JC, NR) and included if they met the criteria relating to the study design described above. No measures of methodological quality were applied in the selection of studies. From the selected studies, the two reviewers independently extracted information on study design, interventions, controls and findings related to adherence and patient outcomes.

Eligible studies varied substantially in their settings, participant selection, medical conditions, interventions, adherence measures and clinical outcome measures, as well as in study quality. For these reasons, quantitative combination of the findings of the studies was not undertaken.

Results

Fifteen trials, reported between 1980 and 2002, were identified that met the review inclusion criteria (*6*, *11–24*) (Table 1 web version only, available at: http://www.who.int/bulletin). In three of these trials, the intervention was a fixed-dose combination pill, while some kind of unit-of-use packaging was used in the other 12 studies. Five studies involved treatments for the control of communicable diseases (tuberculosis (*11–19*), HIV (*14*), leprosy (*15*), malaria (*12*)), three involved combinations of medications to lower blood pressure (*17*, *20*, *22*)), one involved diabetic patients using multiple medications (*13*), one was a trial of vitamin supplementation (*24*), and four tested interventions to improve management of multiple medications by the elderly (*6*, *16*, *18*, *21*, *23*). Seven studies reported clinically relevant or intermediate end-points (*11*, *13*, *14*, *17*, *19*, *20*, *22*) and 13 reported at least one measure of medication adherence (*6*, *11*, *12*, *14–16*, *18–24*). Only one study reported cost of therapy as an outcome (*12*).

Trials of fixed-dose combinations

Two trials compared combination tablets of anti-tuberculosis drugs with the same drugs given separately over the course of 6 months. A study conducted in the USA in 1984–86 with 701 subjects (*19*) found a significant difference in the proportion of patients with sputum conversion at 8 weeks, in favour of the group receiving the fixed-dose combination tablets, but no difference in compliance with medication at 8 weeks or at 6 months (see Table 2 web version only, available at: http://www.who.int/bulletin). Compliance in this study was assessed using a combination of self-reporting, pill counting and urine testing. The other trial involving patients with tuberculosis was conducted in Taiwan, China, in 1997–98 (*11*) and was much smaller, with only 57 and 48 patients in the intervention and control groups, respectively. Differences in sputum conversion at 8 weeks, in compliance, and in radiological improvement at 2 years all favoured the group receiving the fixed-dose combination tablets, but none reached statistical significance. Loss to follow-up was so high in this trial (50%) that slight improvements in adherence amongst those remaining were not considered to be clinically important. The third trial involving fixed-dose combination tablets was in HIV patients (*14*); 223 subjects were randomly selected to have two of their three medications combined in a single tablet. Self-reported adherence and questionnaire scores reflecting adherence behaviours were significantly improved in the intervention group, while clinical outcomes showed a non-significant trend towards improvement. Unfortunately, this trial was powered only to show non-inferiority of the combined pill, which it did, but was too short to adequately assess relevant clinical outcomes.

Trials of unit-of-use packaging

Two trials in economically developing countries were conducted using cluster randomization of health centres to investigate the effect of pre-packaging of medications for infectious diseases (*12*, *15*). Data on clinical outcome were not collected in either of these studies and the clusters were not accounted for in the

analyses. In India, in a trial of calendar-blister packs containing three medications for leprosy (*15*), subjects were followed for 6 months and no differences between groups were found in adherence as assessed by pill counting or urine testing. Significant advantages were found in storage, handling and preservation of medication, and the calendar-blister packs were preferred by staff and users. Pre-packaging of 3-day courses of medication for malaria was tested in Ghana (*12*), with significant improvement in adherence in the group receiving the intervention compared with the control group (82% versus 60.5%), as measured by self-report and medication checks. There was also a 50% reduction in the total cost of treatment, and a 50% reduction in the time spent by patients waiting at the clinic.

The remaining 10 trials were conducted within the health-care systems of economically developed countries. Four trials assessed improvements in compliance with long-term therapy for chronic conditions (hypertension and diabetes) and measured clinically relevant outcomes (*13*, *17*, *20*, *22*); one trial measured adherence to long-term vitamin supplementation for the prevention of disease, using three different measures of adherence (*24*); in five trials, the aim was to reduce the complexity of self-administered medication amongst geriatric patients taking multiple medications, and only adherence was measured (*6*, *16*, *18*, *21*, *23*). All these trials used calendar-blister packaging or a pill organizer, such as the "Dosett box", which is a refillable device with these same basic features. The three studies of hypertension were all of modest size and two were of only 3 months duration. A significant reduction in mean blood pressure in the group receiving the intervention was found in two studies when the use of packaging was combined with patient education and compared with education alone (*17*–*22*), but there was no advantage shown in the third trial (*20*) or where patient education was not used (*22*). One of these trials reported a significant difference between groups in the proportion of patients taking more than 95% of their pills (*22*). Among patients with poorly controlled diabetes, Simmons (*13*) demonstrated a significant reduction in haemoglobin subtype $A1_c$ (HbA_{1c}) and diastolic blood pressure when using calendar-blister packs together with written instructions, in one of the better-designed trials in the review. Although the generalizability of this study is not clear, and no adherence outcomes were measured, it had no major methodological flaws. One small trial tested pill organizers against standard bottles for improving vitamin supplementation (*24*) and found that levels of adherence were very high in both groups over the relatively short follow-up period of 2 months.

All five trials of medication aids for geriatric patients were of poor methodological quality. Four were either too small (*6*, *18*, *23*) or too short (*21*, *23*). The remaining trial (*16*) did not individually randomize patients but allocated the intervention by ward in a repeated crossover design. It appears that the design was not accounted for in the analysis. In three out of five trials, there was a significant improvement in adherence as assessed by pill counting (*6*, *16*, *18*).

Discussion

Despite the considerable importance of improving adherence to effective medications, we found remarkably few large, reliable trials of the effect of combining medications. In all but three out of 15 trials identified, there were trends to improved clinical and/or adherence outcomes. Seven out of 13 studies (53%) reported a statistically significant improvement in adherence to medication, although the outcome measures used were heterogeneous. Four out of seven studies reporting clinical outcomes found a significant improvement in a clinically relevant end-point; one in sputum conversion rate in tuberculosis patients, two in blood pressure, and one study in patients with diabetes showed a reduction in both diastolic blood pressure and HbA_{1c}. Interpretation of these findings is, however, limited by the methodological quality of the studies. Almost all the studies were too small or had inadequate follow-up time, and were therefore likely to miss small to moderate-sized effects. Among the individually randomized trials, the average sample size was only about 150 participants. Trials of this size are only adequate to detect very large improvements in adherence (e.g. would have 90% power at $2P = 0.05$ to detect a change in adherence from 50% to 75%). Clearly, smaller reductions may be worth while from a clinical and public health viewpoint. A trial including about 500 participants would be required to reliably detect an improvement in adherence from 50% to 65%. Also, Haynes (*25*) has suggested that for long-term treatments, studies with initially positive findings need to continue for at least 6 months because of waning adherence over time. Substantial loss to follow-up was common and intention-to-treat analysis was only performed in two trials (*13*, *14*). These two trials, which were the most methodologically rigorous, showed statistically significant improvements in adherence (*14*) and in clinically relevant end-points (*13*). The trial of vitamin supplementation (*24*) recruited volunteers and had very few participants with poor adherence, so any improvements would have been difficult to demonstrate. In the other trials, bias may have resulted from assessing adherence in only those patients sufficiently compliant to remain in this study, and may have reduced the differences between the groups. Subjects were not blind to the interventions and assessors rarely were.

Self-reporting and pill-counting as measures of adherence may have resulted in significant misclassification. As this is usually in the direction of overestimating adherence, it may have also contributed to underestimating of the effect of interventions (*25*). Also, the finding of positive adherence outcomes in studies without clinically important outcome measures has been criticized as having limited relevance for practice (*4*, *25*).

The trials were heterogeneous in their settings, the medical conditions being treated and the outcome measures used. The generalizability of several interventions was unclear, in particular relating to the health-care systems in which they were embedded and the cost-effectiveness of the interventions employed in usual practice. Several authors mentioned the need for economic evaluation, but only one (*12*) reported a comparison of costs.

Fixed-dose combination pills and unit-of-use packaging will have advantages other than increased adherence, and these are likely to be context-specific. Simplification of drug handling and supply, lower packing and shipping costs and prevention of short supply of individual components will be of particular value, especially in developing countries and for treatment of communicable diseases (*11*). Combination medications have the potential to reverse the under-treatment of cardiovascular disease in developed and developing countries (*26*). In many settings, fixed-dose combination pills and unit doses will reduce medication wastage. Reports of individuals having difficulties using blister packs and medication dispensing units (e.g. the Dosett box) are not uncommon in the literature and usually relate to elderly patients (*18*, *20*, *21*). Refinement of delivery mechanisms, patient education, and use of fixed-dose

combination pills where possible could be expected to reduce these barriers.

The paucity of reliable evidence about effective strategies for improving adherence is extraordinary given the investment in assessing the efficacy of separate medications, and the number of individuals taking multiple medications. With respect to therapy-related factors affecting adherence, WHO optimistically suggests that they will be addressed by pharmaceutical companies together with researchers and clinicians (*3*). At present, there seems to be little incentive for companies to invest in combinations of off-patent products that might compete with on-patent monotherapy. The need for development and evaluation of fixed-dose combination products for use in developing countries is particularly marked. ■

Conflicts of interest: none declared.

Résumé

Le recours à des comprimés en association fixe ou à un conditionnement à l'unité améliore-t-il l'observance ? Mise au point systématique

Une observance suffisante des schémas posologiques est déterminante dans le succès du traitement des maladies transmissibles et non transmissibles. Le recours à des comprimés en association fixe ou à un conditionnement à l'unité est une intervention dans le traitement destinée à simplifier les schémas posologiques et à améliorer potentiellement ainsi leur observance. Nous avons réalisé une mise au point systématique d'essais randomisés pertinents afin de quantifier les effets, en termes d'observance du traitement et d'amélioration des résultats, de l'utilisation de comprimés en association fixe et d'un conditionnement à l'unité par rapport à la prescription de médicaments tels qu'ils se présentent habituellement. Seuls 15 essais ont satisfait aux critères d'inclusion : trois d'entre eux étudiaient des comprimés à association fixe, tandis que les 12 autres portaient sur le conditionnement à l'unité. Les essais concernaient le traitement de maladies transmissibles (n = 5), l'administration d'antihypertenseurs (n = 3), le traitement de patients diabétiques (n = 1), la supplémentation en vitamines (n = 1) et la gestion d'une médication multiple par des personnes âgées (n = 5). D'après les résultats des essais, des tendances à l'amélioration de l'observance et/ou des résultats cliniques ressortiraient de tous les essais à l'exception de trois. Ces tendances étaient statistiquement significatives pour quatre des sept essais utilisant un critère de jugement cliniquement approprié ou intermédiaire et pour sept des treize essais rapportant une observance du traitement. Toutefois, les mesures des résultats étaient hétérogènes et l'interprétation se heurtait en outre à des problèmes méthodologiques, en particulier la faible taille de l'échantillon, la durée et le nombre de perdus de vue. Globalement, les éléments disponibles laissent à penser que les comprimés à association fixe et le conditionnement à l'unité sont susceptibles d'améliorer l'observance dans diverses situations, mais les limitations rencontrées dans l'exploitation de ces éléments impliquent qu'il reste des incertitudes quant à l'ampleur des bénéfices.

Resumen

¿Mejoran la observancia las combinaciones de dosis fijas y las tomas preenvasadas? Revisión sistemática

El correcto cumplimiento de las pautas de medicación es fundamental para lograr tratar eficazmente las enfermedades transmisibles y las no transmisibles. Las combinaciones de dosis fijas y las tomas preenvasadas son alternativas terapéuticas concebidas para simplificar los regímenes de medicación y, por tanto, mejorar eventualmente la observancia. Realizamos una revisión sistemática de los ensayos aleatorizados pertinentes para cuantificar los efectos de las combinaciones de dosis fijas y las tomas preenvasadas y compararlos con las formas habituales de presentación de los medicamentos en lo que atañe a la observancia del tratamiento y la obtención de mejores resultados. Sólo 15 ensayos satisficieron los criterios de inclusión; tres de ellos investigaban combinaciones de dosis fijas, y los otros 12 tomas preenvasadas. Los ensayos incluían tratamientos para enfermedades transmisibles (n = 5), uso de antihipertensivos (n = 3), tratamiento de pacientes diabéticos (n = 1), administración de suplementos vitamínicos (n = 1) y manejo de varios medicamentos por personas de edad (n = 5). Los resultados de los ensayos mostraban una tendencia a una mayor observancia y/o mejores resultados clínicos en todos los ensayos menos tres; la mejora alcanzaba significación estadística en cuatro de siete ensayos que informaban de una variable de evaluación clínicamente pertinente o intermedia, y en siete de trece ensayos que informaban del cumplimiento del régimen. Las medidas de los resultados fueron sin embargo heterogéneas, y la interpretación de los datos se vio limitada además por problemas metodológicos, en particular por el pequeño tamaño de las muestras, la corta duración de los estudios y las pérdidas durante el seguimiento. En términos generales, la evidencia acumulada indica que las combinaciones de dosis fijas y las tomas preenvasadas tienden a mejorar la observancia en diversos entornos, pero, debido a las limitaciones de los datos disponibles, persiste la incertidumbre acerca de la magnitud de ese efecto beneficioso.

ملخص

هل تؤدي الحبوب ذات التوليفات الثابتة وإعداد الحزم ذات وحدة الاستخدام إلى تحسين الامتثال للمعالجة؟ مراجعة منهجية

ملخص: يُعَدُّ الامتثال الكافي للنُظُم العلاجية عاملا أساسيا لنجاح معالجة الأمراض السارية وغير السارية، وتُعَدُّ الحبوب ذات التوليفات الثابتة وإعداد حزم الأدوية ذات وحدة الاستخدام من التدخلات العلاجية التي تستهدف تبسيط النُظُم العلاجية، ومن ثمَّ يمكنها أن تحسن الامتثال للمعالجة. وقد أجرينا مراجعة منهجية للتجارب العشوائية المتعلقة بذلك لتقدير الآثار التي تنتج عن أخذ الحبوب ذات التوليفات الثابتة والحزم ذات وحدة الاستخدام، من حيث الامتثال للمعالجة وتحسُّن نتائجها، بالمقارنة مع الشكل المعتاد للأدوية. وقد توافرت في ١٥ دراسة فقط المعايير المؤهلة للإدخال في المراجعة؛ وتم استقصاء حبات الدواء ذات التوليفة الثابتة الجرعة في ثلاث من هذه الدراسات، في حين تم استقصاء الحزم ذات وحدة الاستخدام في ١٢ دراسة أخرى. وقد شملت التجارب معالجة الأمراض السارية (في خمس تجارب)، والأدوية الخافضة للضغط (في ثلاث تجارب)، ومرضى السكري (في تجربة واحدة) والمكملات من الفيتامينات (في تجربة واحدة)، والتدبير العلاجي بأدوية متعددة لكبار السن (في خمس تجارب). وقد أوضحت نتائج التجارب وجود اتجاهات نحو تحسن الامتثال للمعالجة أوتحسن النتائج السريرية أو كليهما في جميع التجارب باستثناء ثلاث منها؛ فقد كانت النتائج يُعتد بها إحصائيا في أربع من التجارب السبع ذات الصلة السريرية، وفي سبع من التجارب الثلاث عشرة المتعلقة بالامتثال للأدوية. وقد كانت مقاييس النتائج متغيرة، وكان تفسيرها محدودا بدرجة أكبر بقضايا تتعلق بمنهجيات البحث، ولاسيَّما صغر حجم العينة وقصر الفترة وغياب المتابعة. وبشكل عام، توضِّح البيِّنات أن الحبوب ذات التوليفة الثابتة والحزم ذات وحدة الاستخدام سيزيدان في غالب الأحوال من تحسين الامتثال للمعالجة في العديد من المواقع، إلا أن محدودية البينات المتوافرة تثير عدم اليقين حول حجم هذه المنافع.

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Table 1. **Methodology of studies reviewed**

Trial	Design	Length of trial	Condition treated	Intervention		Comparison		Clinical outcomes	Adherence outcomes
				n	Exposure	*n*	Exposure		
Su & Perng (2002) (*11*) Taiwan, China	Individual randomization	2 years	Tuberculosis	57	2 months of Ritafer (FDC[a]), with ethambutol 4 months of Rifinah (FDC), with ethambutol (Ritafer = isoniazid, rifampicin, pyrazinamide; Rifinah = isoniazid, rifampicin)	48	Same medications separately, standard packaging	Sputum conversion (%) at 2 and 6 months Radiological improvement (%) at 2 years	Compliant = not lost to follow-up or changed treatment (%)
Geiter et al. (1987) (*19*) USA	Individual randomization	6 months	Tuberculosis	169	2 months of Rifater (FDC) 4 months of Rifamate (FDC) (Ritafer = isoniazid, rifampicin, pyrazinamide; Rifinah = isoniazid, rifampicin)	532	Same medications separately, standard packaging	Sputum conversion (%) at 8 weeks	Composite adherence measures based on urine testing, pill counting, and self-reporting at 8 weeks and at 6 months
Eron et al. (2000) (*14*) USA	Individual randomization	16 weeks	HIV	110	Combivir (FDC) bid with an FDA approved protease inhibitor (Combivir = lamivudine 150/ zidovudine 300)	113	Lamivudine 150 bid[b] Zidovudine 200 tid[c] with an FDA approved protease inhibitor	Treatment failure (increase in viral load) (%) Change in $CD4^+$ cells	Self-reported missed doses (diary cards); patient medication adherence questionnaire (PMAQ) at 8 and 16 weeks
Revankar et al. (1993) (*15*) India	Cluster randomization of 8 centres	6 months	Leprosy	564 (4 centres)	Calendar-blister packs of clofazimine, rifampicin, dapsone	453 (4 centres)	Same medications separately, standard packaging		Pill counting and urine testing at 2, 4 and 6 months
Yeboah-Antwi et al. (2001) (*12*) Ghana	Cluster randomization of 6 centres	3 days	Malaria	314 (3 centres)	Chloroquine and paracetamol pre-packaged in unit doses	340 (3 centres)	Same medications separately, standard packaging		Compliance for 3-day course by home visit/self report
Binstock & Franklin (1988) (*17*) USA	Individual randomization	1 year	Hypertension	30	Refillable calendar pill packs and education programme	32	Bimonthly education programme Standard medication packaging	SBP[d] DBP[e]	
Becker et al. (1986) (*20*) USA	Individual randomization	3 months	Hypertension	86	Calendar-blister packaging	85	Standard medication packaging	DBP reduction at 3 months	Compliance = > 80% pills taken) by pill counting and self-report
Rehder et al. (1980) (*22*) USA	Individual randomization	3 months	Hypertension	25 25	"Dosett box" Refillable 7-day unit-of-use dispenser "Dosett box" plus disease and medication counselling	25 25	Standard medication packaging Standard medication packaging; same counselling	SBP DBP SBP DBP	Pill counting: mean pills taken, % taking > 95% pills Pill counting: mean pills taken, % taking > 95% pills

(Table 1, cont.)

Trial	Design	Length of trial	Condition treated	Intervention		Comparison		Clinical outcomes	Adherence outcomes
				n	Exposure	*n*	Exposure		
Simmons et al. (2000) (*13*) New Zealand	Individual randomization	8 months	Diabetes	36	Calendar-blister pack in medication box with instructions	32	Standard medication packaging, in medication box with instructions	HbA_{1c}[f] SBP DBP	
Huang et al. (2000) (*24*) USA	Individual randomization, factorial design	2 months	Vitamin supplementation	89	Pill organizer 40 active, 49 placebo	94	Standard medication bottles 52 active, 42 placebo		Pill counting: % of pills taken Serum concentrations of vitamin E and vitamin C Self-reporting
Murray et al. (1993) (*6*) USA	Individual randomization	6 months	Geriatric patients with ⩾ 3 medications, in community	9	Unit-of-use packaging, and change to bid dosing	10	Standard medication packaging, and change to bid dosing		Monthly tablet counts, for 6 months
Ware et al. (1991) (*16*) New Zealand	Non-randomized repeated crossover	3 months	Geriatric patients at discharge	45	Calendar-blister pack ("Webster-Pak")	39	Standard medication packaging		Pill counting/ self reporting at discharge, at 10 days, at 1 and 3 months
Wong & Norman (1987) (*18*) USA	Crossover trial	6 months	Geriatric outpatients (2–9 medications)	22	Calendar-blister pack ("C-Pak")	22	Standard medication packaging		Pill counting
Crome et al. (1982) (*21*) UK	Individual randomization	4 weeks	Geriatric patients at discharge	40	Calendar-blister pack ("C-Pak")	38	Standard medication packaging		Pill counting
Crome et al. (1980) (*23*) UK	Crossover trial	10 days	Geriatric patients	26	"Dosett" box Refillable 7-day unit-of-use dispenser	26	Standard medication packaging		Pill counting

[a] FDC = fixed-dose combination pills.
[b] bid = to be taken twice per day.
[c] tid = to be taken three times per day.
[d] SBP = systolic blood pressure.
[e] DBP = diastolic blood pressure.
[f] HbA_{1c} = haemoglobin subtype $A1_c$.

Table 2. **Results of studies reviewed**

Trial	Condition	Clinical outcomes	*P*-value	Adherence outcomes	*P*-value	Methodological limitations
Su & Perng (2002) (*11*) Taiwan, China	Tuberculosis	Sputum conversion: At 2 months, 95.0% vs[a] 88.9% At 6 months, 100% vs 100% Radiological improvement: At 2 years, 92.3% vs 84.0%	> 0.05 — > 0.05	Compliance (not lost to follow-up or changed treatment) At 6 months, 70.2 % vs 66.7%	 > 0.05	Large loss to follow-up (50% by 2 years) Intention-to-treat analysis not reported
Geiter et al. (1987) (*19*) USA	Tuberculosis	Sputum conversion: At 8 weeks, 86.6 vs 77.7% Absolute difference, 8.9% (95% CI[b], 1.1–16.7)	< 0.05	Urine testing, pill counting, self-reporting: At 8 weeks, 96.5% vs 98.1% fully compliant; At 6 months; 88.5 vs 87.3 % fully compliant	> 0.05 > 0.05	Exposure and comparison groups enrolled at different times Exclusions post-randomization plus loss to follow-up = > 30% Intention-to-treat analysis not reported Composite compliance measure not well described
Eron et al. (2000) (*14*) USA	HIV	Treatment failure (viral load): 3.6 vs 7.1 % Absolute difference = 3.5% (95% CI, -2.4–9.3%) Change in $CD4^+$ cells: Treatment difference = 5.9 (95% CI,-15.8–27.6) cells/litre	0.26 0.59	Self-reported missed doses (diary cards): > 98% compliance for both groups Fewer missed doses of lamivudine/zidovudine: At 8 weeks At 16 weeks Adherence questionnaire: Better scheduling and timing scores: At 8 weeks At 16 weeks Better total scores: At 8 weeks At 16 weeks	 0.007 0.046 < 0.001 0.022 0.002 0.020	Powered to show only non-inferiority of clinical outcomes for fixed-dose combinations Too short in duration to determine adherence to long-term treatment
Revankar et al. (1993) (*15*) India	Leprosy			Compliance (correct pill count): At 2 months, 86% vs 87% At 4 months, 87% vs 89% At 6 months, 91% vs 88% Urine testing (three tests): 86–94% vs 83–95%	 — — — —	All participants followed up by pill counting, but urine testing at follow-up for 59% of participants at 2 months, 42% of participants at 4 months, 19% of participants at 6 months. Cluster design not considered in analysis
Yeboah-Antwi et al. (2001) (*12*) Ghana	Malaria			Compliant for 3 days: Tablets, 82.0% vs 60.5% Absolute difference = 21.5% (95% CI, 11.8–31%) Syrup, 54.7% vs 32.6% Absolute difference = 22.1% (95% CI, 8.3–36%) Total, 72.1 vs 49.8% Absolute difference = 22.3% (95% CI, 14.1–31%)	 < 0.001 < 0.001 < 0.001	Precision of estimates not adjusted for cluster design Loss to follow-up: 16% in group receiving the intervention, 27% in control group

(Table 2, cont.)

Trial	Condition	Clinical outcomes	*P*-value	Adherence outcomes	*P*-value	Methodological limitations
Binstock & Franklin (1988) (*17*) USA	Hypertension	SBP[c] and DBP[d] after 1 year: Reduction in mean DBP, 9 mmHg vs 1 mmHg (1.2 vs 0.13 kPa) Reduction in mean SBP, 15 mmHg vs 3 mmHg (2.0 vs 0.40 kPa)	< 0.01 < 0.01			Little detail about pill dispensing pack Inconsistency between results in text and results in Fig. 1 Small numbers Loss to follow-up not reported
Becker et al. (1986) (*20*) USA	Hypertension	Reduction in DBP at 3 months: 1.0 vs 0.8 mmHg (0.13 vs 0.11 kPa)	> 0.05	Pill counting (compliance = > 80% of pills taken) 84.0% vs 75.3 % Self-reported compliance improved 2.4% vs 3.5%	> 0.05 > 0.05	Too short in duration to determine adherence to long-term treatment Loss to follow-up, 8% Intention to treat analysis not reported
Rehder et al. (1980) (*22*) USA	Hypertension	SBP: no change in either group DBP: increase, 5 vs 6 mmHg (0.67 vs 0.80 kPa) SBP: no change DBP reduction, 12 vs 4 mmHg (1.6 vs 0.53 kPa)	< 0.02	Pill counting 95% vs 88% pills taken 88% vs 48% took over 95% pills Pill counting 99% vs 90% pills taken 92% vs 60% took over 95% pills	> 0.05 < 0.01 > 0.05 < 0.01	Too short in duration to determine adherence to long-term treatment Small numbers Loss to follow-up, 28% Intention-to-treat analysis not reported
Simmons et al. (2000) (*13*) New Zealand	Diabetes	HbA_{1c}[e] (%) -0.95 ± 0.22 vs -0.25 ± 0.25 SBP: -3.6 ± 2.3 vs –2.6 ± 2.8 mmHg (–0.48 ± 0.30 vs –0.35 ± 0.37 kPa) DBP : -5.8 ± 1.5 vs 0.1 ± 1.9 mmHg (0.77 ± 0.2 vs 0.01 ± 0.25 kPa)	0.026 0.89 0.0041			
Huang et al. (2000) (24) USA	Vitamin supplementation			Pill counting: 100% vs 99% of pills taken 91% vs 94% took over 90% pills Serum levels: Mean difference in serum levels of vitamin C between intervention and placebo group was similar for FDC[f] and non-FDC Lower serum levels in intervention group for vitamin E Self-reporting: no difference	> 0.05 > 0.05 0.47 0.06 0.30	Over-dosing not counted as non-adherence No over-dosing in pill organizer group vs 2.4% in control group Intention to treat analysis not reported, but little loss to follow-up and reasons unrelated to use of pill organizer Too short in duration to determine adherence to long-term treatment Very high adherence in both groups
Murray et al. (1993) (*6*) USA	Geriatric patients with ⩾3 medications			Pill counting (compliance = pills taken/pills dispensed): 92.6% (95% CI, 88.5–96.7) vs 82.6% (95% CI, 78.7–86.5)	0.001	Very small numbers Loss to follow-up, 20% Intention-to-treat analysis not reported

(Table 2, cont.)

Trial	Condition	Clinical outcomes	*P*-value	Adherence outcomes	*P*-value	Methodological limitations
Ware et al. (1991) (*16*) New Zealand	Geriatric patients at discharge			Pill counting (all pills taken): 86.7% vs 66.7% at discharge; 68.8% vs 41.0% at 10 days; 64.4% vs 38.5% at 1 month; 48.9% vs 23.1% at 3 months	 0.03 0.02 0.03 0.03	No randomization Allocation by ward as a cluster Repeated crossover design Too short in duration to determine adherence to long-term treatment Cluster design not considered in analysis. Loss to follow-up, >30% Intention to treat analysis not reported
Wong & Norman (1987) (*18*) USA	Geriatric outpatients (2–9 medications)			Pill counting (non-compliance index = incorrect doses/total doses): Average non-compliance index, 2.04 vs 9.17	< 0.01	Not randomized, crossover design Small numbers Loss to follow-up, 22%
Crome et al. (1982) (*21*) UK	Geriatric patients at discharge			Pill counting (error = tablets not taken/total tablets): 26.2 vs 26.1% error	—	Too short in duration to determine adherence to long-term treatment
Crome et al. (1980) (*23*) UK	Geriatric inpatients			Pill counting (error = tablets not taken/total tablets): Mean error 6.2% vs 8.5 %	> 0.05	Too short in duration to determine adherence to long-term treatment Small numbers Subjects were inpatients

[a] vs = versus.
[b] CI = confidence interval.
[c] SBP = systolic blood pressure.
[d] DBP = diastolic blood pressure.
[e] HbA_{1c} = haemoglobin subtype $A1_c$.
[f] FDC = fixed-dose combination pills.